Neurology

OFFICIAL JOURNAL OF
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SEPTEMBER--1956
Volume 6 — Number 9

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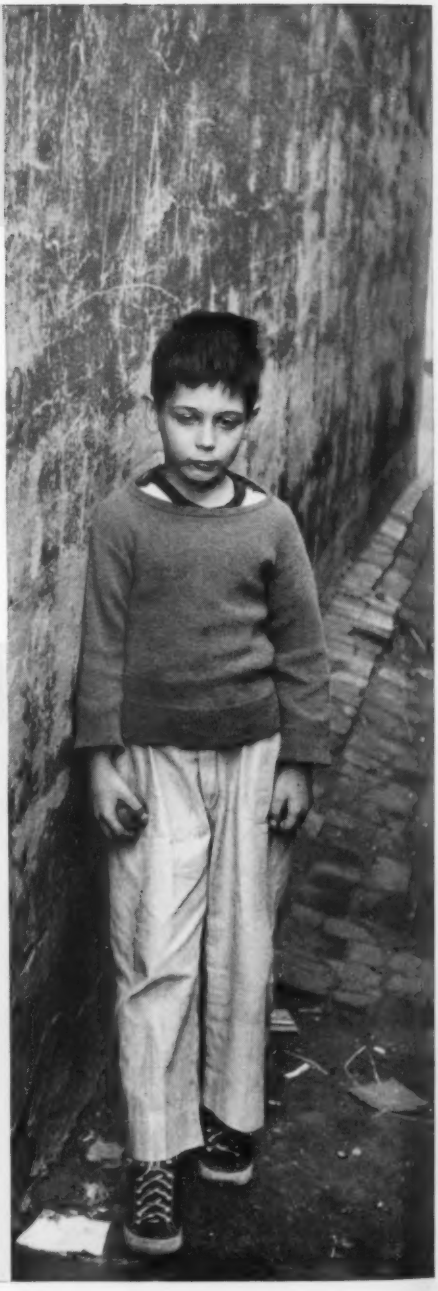

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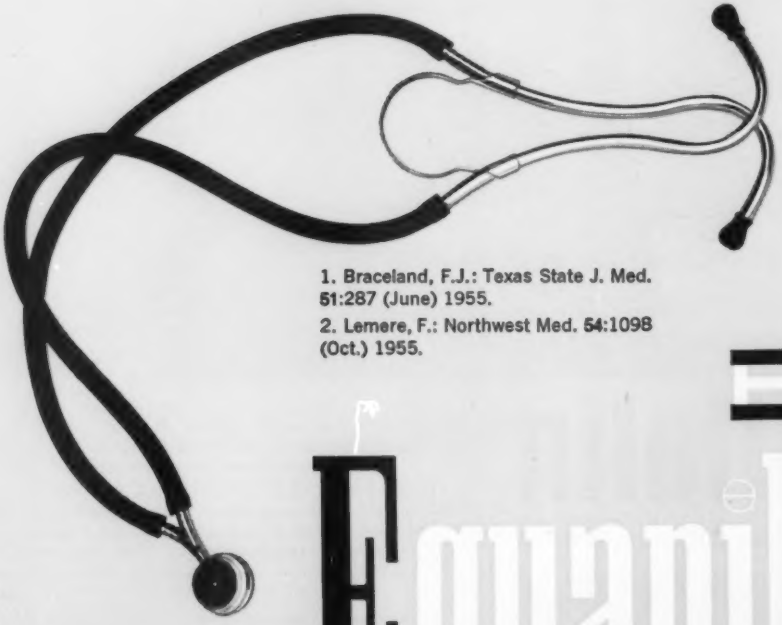

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2. Lemere, F.: Northwest Med. 54:1098 (Oct.) 1955.

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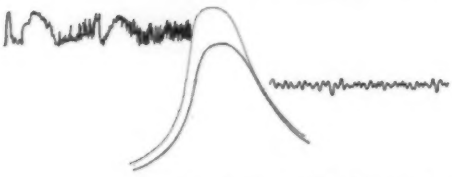

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1. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Livingston, S., and Petersen, D.: To be published.
3. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

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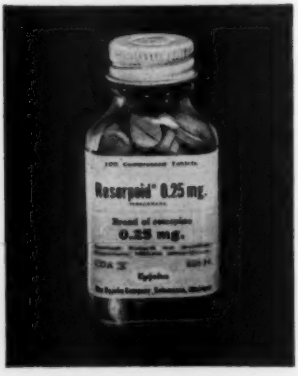

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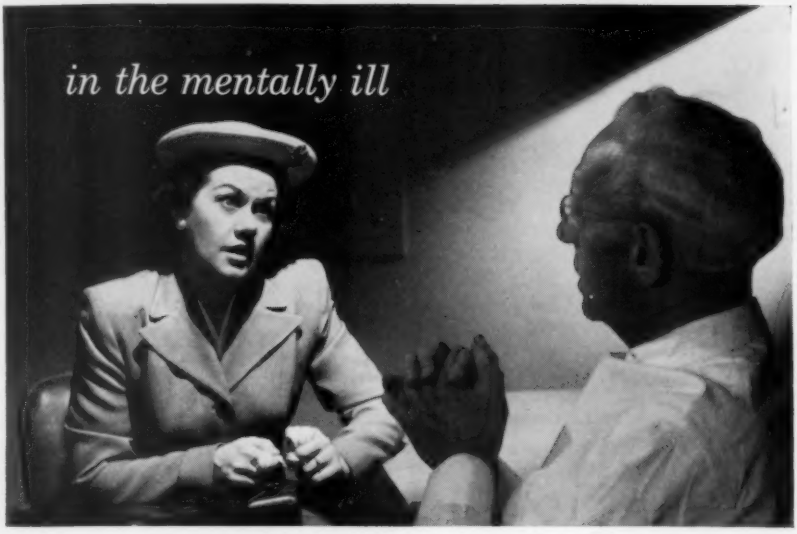

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1. Hollister, L. E., Krieger, G. E., Kringel, A., and Roberts, R. H.: Ann. New York Acad. Sc. *61*:92 (April 15) 1955. 2. Hoffman, J. L., and Konchegul, L.: Ann. New York Acad. Sc. *61*:144 (April 15) 1955. 3. Kline, N. S., and Stanley, A. M.: Ann. New York Acad. Sc. *61*:85 (April 15) 1955.

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1. Yohe, C.D.: in Chlorpromazine and Mental Health, Philadelphia, Lea & Febiger, 1955.

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Volume 6 Neurology Number 9

Pseudotumor Cerebri

Benign Intracranial Hypertension

Leo M. Davidoff, M.D.

In spite of continuing experience with problems involving increased intracranial pressure, one phenomenon has remained puzzling and unsolved. This is the group of cases of individuals presenting themselves with evidence of increased intracranial pressure in the form of headache and papilledema, but who usually show no other abnormal neurologic signs except occasionally one or both sixth nerve palsies, spinal fluid the pressure of which is elevated but in which the cell eount and protein content are usually normal, and normal pneumoencephalograms. It is extremely difficult to know how to designate these cases, primarily because the etiology is still unknown.

As will develop later, cogent reasons can be evoked against the terms "serous meningitis," "otitic hydrocephalus," "hypertensive meningeal hydrops," "mural sinus thrombosis," and perhaps the only safe way to deal with the problem up to the present time would be to refer to it as "pseudotumor" or to accept the suggested designation of Foley[1] of "benign intracranial hypertension."

In 1936 and 1937 Davidoff and Dyke[2,3] published a series of 15 cases falling into this category, all of which were suspected of harboring brain tumors and in all of which a mass lesion was excluded by pneumoencephalography (ventriculography and/or encephalography). This was the first reported series of such cases in which a diagnosis of tumor was excluded by the demonstration of a normal ventricular system. In 1937 also a series of 22 similar cases was published by Dandy.[4] Most of our patients were treated by subtemporal decompression, and we were impressed by the appearance of large quantities of clear, colorless cerebrospinal fluid welling up out of widened and deepened subarachnoid spaces at the time of operation

*From the department of surgery, Albert Einstein College of Medicine, New York City.

until the brain which, at the moment when the dura was opened, bulged dangerously through the dural defect, had fallen back well beneath the dural margins simply as a result of escape of fluid.

After reviewing the numerous theories put forth to explain the nature of this condition, none of which seemed to fit entirely all the cases, we fell back upon what seemed to us two uncontroversial facts: 1) increased intracranial pressure, and 2) excessive fluid in the meninges. We suggested the term "hypertensive meningeal hydrops" for this condition.

REVIEW OF LITERATURE

The pertinent literature on this subject was reviewed up to 1937 in our report[3] on hypertensive meningeal hydrops. Since then a considerable number of papers have appeared, many of which simply reported a case or two. A number of contributions, however, have added facts or reflections on this still largely unexplained syndrome.

The occurrence of lateral sinus thrombosis as an etiologic factor in this condition came under critical scrutiny in a number of reports. Hamberger,[5] whose 14 year old female patient developed this disease following mastoiditis, cast doubt upon it. The original operation for mastoid disease included exploration of the sinus which showed no evidence of thrombosis. Papilledema occurred a month later. The wound was reopened, the sinus was explored, and no thrombosis was found. Further, McKenzie[6] called attention to the fact that lateral sinus thrombosis is a very common condition and yet the syndrome under present discussion is relatively quite rare, leading him to conclude that not all cases of sinus thrombosis are followed by intracranial hypertension, nor that every case of the latter is due to lateral sinus thrombosis. Among other data, Wagener[7] brought together a number of reports proving that lateral sinus thrombosis could be responsible for some of these cases, provided the larger of the two lateral sinuses were involved, usually the right, but that obviously this does not account for the majority of cases.

A very important concept as to the etiology of this condition has been the thrombosis of the *superior* longitudinal sinus. In an exhaustive review of the literature on "pseudotumor cerebri," Wagener traced the development of this concept in the literature.

The first attempt to demonstrate involvement of the superior longitudinal sinus was made by Frenckner[8] when, in a case of this disease following mastoiditis, a sinogram was attempted in the posterior part of the superior longitudinal sinus but no blood was obtained, thus indicating a thrombosis in this vessel. This was confirmed later by carotid angiograms which revealed in the venous phase an obstruction in the posterior part of the superior longitudinal sinus. In 1937 also Bailey and Hass,[9] in a case of lateral sinus thrombosis, demonstrated at postmortem examination a propagation to the superior longitudinal sinus which had resulted in the obstruction of tributary cerebral veins, with hemorrhage and necrosis in the brain area involved. Symonds[10] in the same year was led to conclude that, while lateral sinus thrombosis probably does not account for the syndrome of what he then termed "otitic hydrocephalus," the propagation of a clot from a lateral sinus thrombosis into the su-

perior longitudinal sinus may put out of action a sufficiently large proportion of arachnoid villi, causing the otitic hydrocephalus. He felt that, anatomically, superior longitudinal sinus thrombosis should occur more frequently with involvement of the right lateral sinus rather than the left, and in a collection of 26 cases of otitic hydrocephalus following unilateral otitis media, the right ear was involved in 17 and the left in nine cases. He explained the absence of blood in the cerebrospinal fluid in cases of "otitic hydrocephalus," if due to superior longitudinal sinus thrombosis, by the fact that these are cases in which the thrombosis takes a more benign clinical course. Those cases of superior longitudinal sinus thrombosis in which tributary cerebral veins become involved with extensive necrosis and subarachnoid hemorrhage are usually fatal. Symonds was further led to implicate the superior longitudinal sinus rather than the lateral sinuses by demonstrating three cases of so-called "otitic hydrocephalus" in which the infection was elsewhere in the body than in the middle ear.

The first systematized attempt at testing this theory was made by Ray and Dunbar,[11,12] when they began to carry out sinusography by placing a burr hole over the superior longitudinal sinus and injecting Diodrast directly into this structure. Experience with one patient formed the subject of a report in the earlier paper. They successfully treated the patient by removal of an organized thrombus from the superior longitudinal sinus, following this by a course of anticoagulation therapy. They concluded that obstruction to venous drainage was probably responsible for the syndrome of "pseudotumor" because 1) bilateral neck dissection and bilateral ligation of the jugular vein frequently result in papilledema, headache, diplopia, and increased cerebrospinal fluid pressure which may persist for some time; 2) ligation or resection of the posterior two-thirds of the superior longitudinal sinus for the removal of parasagittal meningiomas may result in coma and death due to massive congestion and hemorrhagic edema of both hemispheres; and 3) thrombosis of the superior longitudinal sinus has been demonstrated at necropsy in cases of pseudotumor cerebri. Sinusography carried out in four consecutive cases revealed occlusion of the superior longitudinal sinus in three and occlusion of the dominant transverse sinus in the fourth case. They then predicted that most cases of this sort would prove to be due to thromboses of the superior longitudinal sinus or major transverse sinus. They did not agree with Symonds that the superior longitudinal sinus must necessarily be implicated, but stated that, if the lateral sinuses were unequal in size so that the smaller of the two, usually the left, were inadequate and the larger were involved by a thrombus, the same result could occur. They suggested that, in cases of increased intracranial pressure with papilledema, normal ventricles as demonstrated by ventriculography, and normal cerebrospinal fluid chemistry, sinusography should be undertaken in accordance with the technic of Ray, Dunbar, and Dotter,[13] and if thrombosis is demonstrable, anticoagulant therapy should be undertaken. Following this report on sinusography, it appeared that the long controversy over the etiology of the "pseudotumor" syndrome was largely solved, that the condition was mechanical due to ob-

struction to the cerebrospinal fluid by thrombosis of the superior longitudinal sinus or occasionally the major transverse sinus, and that the thrombosis was usually due either to a middle ear infection, an infection elsewhere in the body, or some other less well known cause for sinus thrombosis.

In pursuit of this problem, Ray and his co-workers continued to perform sinusography in cases of "pseudotumor," and at the meeting of the Harvey Cushing Society in 1955 Ray[14] was able to report on 28 cases. Their initial success in demonstrating venous sinus thromboses by sinusography in these cases did not hold up, since they were able to demonstrate evidence of thromboses in only ten of 24 sinograms. Ray felt that, in the cases in which dural venous sinus thrombosis, especially of the superior longitudinal sinus in its posterior aspect, was demonstrable, this condition stands in etiologic relationship to the symptoms of increased intracranial pressure, but that obviously in a high percentage of "pseudotumor cerebri" this etiology cannot be responsible for the condition. This left us once more with a clinical syndrome, many examples of which are produced not only by unknown etiologic factors, but even by an unknown mechanical or chemical mechanism.

Having followed the question of venous sinus thrombosis more or less to a dead end, one is then inclined to return once more to a consideration of other factors as etiologically related to this condition. Dandy,[4] in reporting 22 cases in 1937, felt that, because of the normal size of the ventricles, the fluid must be within the brain rather than in the cerebrospinal fluid spaces, or that, as a result of vasomotor influences, increased intracranial pressure is produced by dilatation of the vascular bed intracranially. Sahs and Hyndman[15] concluded that the condition is caused by "cerebral edema" due perhaps to toxic origin. Yaskin, Groff, and Shenkin[16] were unable to reconcile the alert mental state of these patients with generalized edema of the brain and thought that the increased intracranial pressure was due to "alterations of cerebrospinal fluid circulation and/or chemical composition of the fluid, the nature of which is unknown." Because a patient coming under their observation seemed to respond favorably to treatment with Benadryl, Devanney and Shea[17] were inclined to invoke allergy as an etiologic factor.

Observing that 71.4 per cent of 42 cases, including those of Dandy,[4] Davidoff and Dyke,[2,3] and Sahs and Hyndman,[15] were women, Wagener[7] speculated concerning the association of increased intracranial pressure in these cases with "menstrual edema." He quoted a report of Thomas[18] of a 38 year old woman who not only had severe generalized edema with a gain of 11 to 14 pounds in weight with each menstrual period but also developed blurred vision, choked disks, and headache, all of which disappeared with the spontaneous occurrence of diuresis. McCullagh[19] reported the case of a 24 year old woman with a similar history. Both of these cases were treated successfully with pregnancy urine extract.

In an exhaustive review of the literature, Foley[1] culled 46 cases which he considered examples of "otitic hydrocephalus." However, he felt that no satisfactory evidence of mural thrombophlebitis of the superior longitudinal sinus with impairment of absorption of cerebrospinal fluid was responsible for

the raised pressure. Moreover since the ventricles were of normal size, he believed that the term "hydrocephalus" was incorrect. In his estimation such radiologic and pathologic evidence as is available suggests that the cause is thrombosis of a lateral sinus, if it happened to be the major one. He felt that a process of cerebral edema may contribute to the raised intracranial pressure, since canalization of a thrombosed sinus occurs in a few weeks, whereas intracranial hypertension in these cases may last for many months.

In addition to the 46 cases with histories of ear or mastoid infection, Foley[1] also collected 60 cases from the literature in which a prolonged episode of intracranial hypertension with a normal ventricular system existed without any evidence of preceding infection elsewhere in the body. These were more than twice as common in women as in men and showed earlier failure in vision than the cases of otitic hydrocephalus or cerebral tumor. The evidence of dural sinus thrombosis in these cases was extremely scanty, and he felt that the absence of ventricular dilatation made it improbable that overproduction of cerebrospinal fluid caused the condition. He stated that "the deep subarachnoid spaces often found at craniotomy were an artifact caused merely by opening of the skull."

In a second part of his paper, a study of 95 cases with "papilledema" of obscure origin in his own experience was reviewed. Thirty-five of these were discarded because they did not seem to fit into the picture of increased intracranial pressure. The remaining 60 cases he was able to divide into three groups: 1) otitic cases in which he felt thrombosis of the major lateral sinus was the probable cause of increased intracranial pressure; 2) a larger group in which there was no history of infection or injury, consisting almost exclusively of females with the peak incidence in the fourth decade; and 3) a smaller group in which the condition occurred following infection elsewhere than in the ears or mild head injury, in which group the sexes were equally affected and the age of onset was usually lower than in the second group. Foley thought that very little evidence existed that thrombosis of the superior longitudinal sinus is responsible for the condition in either the second or the third group. He found obesity a common feature and also some association with pregnancy and miscarriage in the second group. He showed that electroencephalograms, especially in the second and third groups, were for the most part normal, in which sense they differed from those due to increased intracranial pressure resulting from brain tumor, and he produced some evidence to indicate that with the latter, the slow activity usually seen is associated with a fall of cerebral blood flow, which apparently does not take place in cases of "pseudotumor."

AUTHOR'S MATERIAL

Since the publication of our paper in 1937 when 15 cases were reported, an additional 46 cases have been studied for diagnosis and treatment. All of these patients had true papilledema, most of them complained of headaches, and many of them had failing vision. All but one had normal ventricular systems as demonstrated by pneumoencephalography (either ventriculography or lumbar encephalography). The spinal fluid was otherwise within normal limits as

TABLE 1

NINE CASES WITH PRECEDING EAR OR MASTOID INFECTION

Age	Male	Female	Total
0 to 5		1	1
6 to 10	2	3	5
11 to 20	1		1
21 to 25			
26 to 30			
31 to 35			
36 to 40		1	1
41 to 45	1		1
46 to 50			
Over 50			
Total	4	5	9

TABLE 2

23 CASES WITH HISTORY OF INFECTION OTHER THAN OTITIC OR TRAUMA

Age	Male	Female	Total
0 to 5	2		2
6 to 10	4		4
11 to 15		3	3
16 to 20	1	2	3
21 to 25	1	2	3
26 to 30		1	1
31 to 35	1		1
36 to 40			
41 to 45	1	2	3
46 to 50		2	2
51 and over	1		1
Total	11	12	23

far as cell count and protein were concerned. Many of them had complained of diplopia, and these usually showed interference with one or both sixth cranial nerves. When these two groups are combined, our total experience with this condition is based upon 61 cases.

In order to compare experiences, the author has subdivided these 61 cases into groups similar to those which Foley described. Of the 61 cases, nine (four males and five females) developed their symptoms following otitis media, and would thus be classified as otitic cases (table 1). Twenty-three cases (11 males and 13 females) developed their symptoms following infections elsewhere in the body than in the ears and mastoids or after a head trauma. This series would correspond to Foley's group three, in which he also noted that the sexes are relatively equally represented (table 2). Finally the last group, in which no history of infection or injury was elicited, is similar to Foley's group two (table 3). While this group in the author's series included 18 females and 11 males, it was by no means "almost exclusively consisting of females," but the peak of incidence was also in the fourth decade. In three of the 18 women in this group, unusual obesity was noted. There were none whose illness began in association with pregnancy or miscarriage. Table 4 shows a combination of Foley's group two and the author's similar group three, a total of 89 cases, of which females outnumber males two to one.

In the light of developments since 1937 and the study of a total of 61 cases, the author is inclined to agree with Foley's conclusions concerning the etiology of the condition under discussion, namely that a relatively small number of cases are associated with middle ear or mastoid infection and would thus properly belong to the group designated by Symonds as "otitic hydrocephalus," while the other cases may be associated with infection or trauma elsewhere in the body and are probably not connected with venous thrombosis but perhaps represent manifestation of toxic changes secondary to an infection elsewhere in the body or trauma to the nervous system. In the third group, the etiology of which is unknown, some cases at least may be associated with electrolyte imbalance,

TABLE 3

29 CASES WITH NO HISTORY OF INFECTION OR TRAUMA

Age	Male	Female	Total
0 to 5		1	1
6 to 10	1	2	3
11 to 15	1	1	2
16 to 20		3	3
21 to 25		2	2
26 to 30	1	3	4
31 to 35	1	2	3
36 to 40	4	1	5
41 to 45	2	1	3
46 to 50		1	1
51 and over	1	1	2
Total	11	18	29

TABLE 4

89 COMBINED CASES OF FOLEY GROUP 2 AND DAVIDOFF GROUP 3

Age	Male	Female	Total
0 to 5	0	1	1
6 to 10	2	6	8
11 to 15	4	8	12
16 to 20	1	9	10
21 to 25	3	13	16
26 to 30	2	7	9
31 to 35	2	7	9
36 to 40	7	3	10
41 to 45	5	4	9
46 to 50	1	2	3
51 and over	1	1	2
Total	28	61	89

particularly in female patients. The latter two groups, making up the majority of the total number, may be designated as "benign intracranial hypertension" at least until the mechanism producing the syndrome is better understood.

ELECTROENCEPHALOGRAMS

Electroencephalographic studies were available in most of the author's cases after 1937, and in conformity with Foley, a majority of them showed electrical recordings interpreted as within normal limits. Five instances in which diffuse abnormalities varying from slight to relatively marked slowing with high amplitude all belonged to the group in which infection or trauma preceded the onset of the illness.

TREATMENT

Whatever the underlying cause and however the syndrome develops, the immediate danger faced by these patients is the possibility of visual impairment. In cases in which the papilledema is advanced or visual acuity is threatened, which makes up the majority of instances, the most immediately effective form of therapy, namely subtemporal decompression, should be carried out. Thus in our series of 61 cases, subtemporal decompression was performed in 51 and suboccipital decompression in one case. In nine instances treatment consisted of dehydration measures and repeated lumbar puncture followed by a salt-poor diet, limitation of fluid intake, and ammonium chloride or Diamox administration. Recovery occurred in the majority of cases.

Except for four cases which could not be traced, follow-up observations were continued for from one to 22 years. With the exception of the following complications, all patients recovered from the operation and eventually from their disease. One died two months after leaving the hospital from an unknown cause. Postmortem examination of his brain showed no abnormalities.

COMPLICATIONS

Case 1. One patient, a boy of eight, who was seen 11 weeks after the onset of double vision which appeared in the course of mastoid infection, showed a high degree of bilateral papilledema with bilateral sixth nerve palsy. Ventriculography showed his ventricles to be within normal limits in size, without any

distortion, and a left subtemporal decompression was done (he was left-handed). The papilledema did not subside for several months, and he required repeated lumbar puncture as well as dehydration measures. He eventually got well and remained so for a period of 16 years, when he developed convulsive seizures. At this time electroencephalograms were done for the first time in his case, and showed some slowing of activity at the site of his old decompression. The seizures were brought under control with the aid of Dilantin. While the appearance of seizures in this case was long delayed, it may nevertheless be ascribable to trauma or adhesions in the area of the decompression.

Case 2. One other patient who came to us with severe headache and diplopia of four weeks' duration, without any preceding otitis media or infection elsewhere in the body, was at that time an 18 year old girl, moderately obese, who showed a severe degree of papilledema with exudates and hemorrhages. Ventriculography was attempted but the ventricles were so small that no gas remained. A subtemporal decompression was done and eventually postoperatively pneumoencephalograms, which showed a normal ventricular system. Four years postoperatively she had a single convulsive seizure, which has never recurred. She has been followed for a total of 16 years, was married at 23 years of age, and has had two children. There have been no miscarriages. Her pregnancies have been entirely normal. She has remained well. Electroencephalograms following the convulsion and on several occasions since then have been negative. In this case the occurrence of a single epileptic seizure does not appear to have been related to the decompression, and may or may not have been associated with the unknown factor which caused her disease in the first place. In the period of 12 years after the seizure and without anticonvulsant medication, no other epileptic episodes have occurred. No other cases of seizures occurred in our series.

Case 3. Another obese young woman, 32 years of age, with a history of three months of headache and one month of blurred vision, presented herself with a marked degree of papilledema. No history of otitis media or other known infection existed. Attempted ventriculography in her case also was unsuccessful because of the small size of the ventricles. Subtemporal decompression revealed "a wet brain." Her headaches disappeared and the papilledema gradually subsided. Four years following decompression, she was entirely well. Two years later, however, her decompression became tense and blurring of the disk margins recurred. There were no other neurologic signs. The patient was offered hospitalization and restudy of her case, but she decided against this and her eventual fate is unknown. Whether she had suffered from a recurrence of her original illness or had had a slowly developing tumor from the beginning is, of course, unknown.

Case 4. A 15 year old boy with a history of mild ear infection as a child came to us three weeks after the onset of headaches and occasional vomiting. He had bilateral papilledema, an initial pressure on lumbar puncture of 440 mg., and a spinal fluid total protein content of 35 mg. per cent. Ventriculograms revealed a normal ventricular system. A subtemporal decompression was done, and he was discharged improved from the hospital. Two months later he returned with a recurrence of headache, reelevation of his optic disks, a tense decompression, and a slight left-sided hemiparesis. Our first impression was that the patient's original lesion was a tumor which, at the time of ventriculography, was not big enough to produce deformity of the ventricular system, but that it had increased in size since the decompression. Ventriculography was, therefore, repeated. Only small quantities of fluid under very high pressure were obtained from each side, and only a few cc. of gas could be injected. The resulting films showed gas in the left ventricle only, but this appeared to be displaced from right to left. Lumbar puncture following ventriculography showed blood-tinged fluid with yellowish supernatant fluid after the cells had settled down. Cerebral angiography was then carried out, which revealed a marked depression and lengthening of the middle cerebral vessels, indicating a mass above the location of the Sylvian fissure on the right side. A right frontotemporal flap was then made, utilizing the scar in the temporal region as the posterior limb of the new incision. After the scalp was opened and several burr holes were made preparatory to the turning of a bone flap, the dura was found markedly discolored as seen

through the several burr holes. This led us to suspect a subdural hematoma. The dura was, therefore, opened through one of the burr holes, which caused the discharge of a large quantity of black, changed blood. Further exploration then revealed well formed membranes of a subdural hematoma, with very little solid blood clot. Following evacuation of the clot, the patient recovered and has remained well since.

Case 5. The following is a case showing not so much a complication of therapy as an unusual variation of this disease. A young overweight 18 year old girl with a history of poor vision showed unsteadiness of gait, lack of balance, incoordination, and papilledema. Ventriculograms revealed a moderately dilated but otherwise normal ventricular system. The ventricular fluid protein was 7 mg. per cent. Electroencephalograms were within normal limits except for slight slowing upon hyperventilation. She was, nevertheless, suspected of having a possible cerebellar tumor. A suboccipital exploration was carried out, which was entirely negative. The patient was discharged from the hospital markedly improved and has been followed for a period of five years, during which time she has remained completely well.

Case 6. The following case was the most recalcitrant to treatment in the entire series. A 44 year old married woman complained of headaches and diminished visual acuity, without any history of otitis media or other known infection or trauma. Her symptoms were of two months' duration, and her only abnormal signs were bilateral papilledema. She was referred to a medical neurologic colleague who carried out pneumoencephalography which showed a normal ventricular system. The initial pressure on lumbar puncture was 220 mg. and the total protein content was 24 mg. per cent. A right subtemporal decompression was carried out. Her headaches diminished in intensity and the papilledema began to subside by the time she was discharged from the hospital. A month later the papilledema had subsided somewhat more than at the time of her discharge. She was still complaining of pain in her head, and the decompression was full and tense, although her vision was better. She was placed on a salt-free diet, fluids were limited to 1,500 cc., and ammonium chloride was prescribed, 3 gm. three times daily, three days on and two days off. The condition remained more or less static, with a moderately bulging decompression, some residual papilledema, and some headache in spite of the continued salt-free diet, limitation of fluids, and ammonium chloride therapy. About 22 months after the decompression, the patient developed "terrific headaches," although the decompression and the papilledema did not show any considerable degree of increase.

In view of the patient's complaints, she was readmitted to the hospital in June 1953, and examination was essentially unchanged. The electroencephalograms showed a slight degree of diencephalic dysfunction and a somewhat greater degree of focal abnormality in the right temporal area at the site of the decompression. Her lumbar puncture at this time revealed an initial pressure of 150 mm. The removal of 25 cc. of crystal clear fluid diminished the bulging in the right subtemporal area. The total protein in the cerebrospinal fluid was 22 mg. per cent. A subarachnoid-peritoneal anastomosis was then performed with the use of a polyethylene tube. Immediately postoperatively the decompression became soft and flat, and the patient was entirely relieved of her headaches. She was discharged from the hospital on the seventh postoperative day.

This seemed to be the end of her troubles, but five months later she began to have pain chiefly in her right leg and in the rectum, which did not yield to symptomatic treatment. Meanwhile her decompression remained soft and the papilledema had completely disappeared, although some secondary atrophy was demonstrable. The pain in her lower extremities continued; 18 months after the anastomosis, the laminectomy scar was reopened and a small dural defect was found, through which a sensory nerve root was herniating. This was reposited and the tiny defect in the dura was closed, with complete relief of the symptoms referable to her lumbar region.

It now seemed to us that we had finally reached a state of satisfactory recovery, but the patient began to complain of local pain at the site of the decompression which was soft and scaphoid, and on examination there was marked tenderness over the margins of the bony defect. She was, therefore, readmitted to the hospital, and two and a half months after the last operation, a stainless steel plate was inserted to cover the defect in the skull

in her right subtemporal region. At last, for nearly a year, the patient has been reasonably comfortable although her continued invalidism has made her somewhat hypochondriacal, and she is herself not ready to concede that her troubles are wholly at an end.

SUMMARY AND CONCLUSIONS

Pseudotumor cerebri is defined as a syndrome of increased intracranial pressure producing headache and papilledema, usually without other neurologic manifestations. The cerebrospinal fluid is under increased pressure but shows a normal total protein content and normal cell count. The pneumoencephalograms are within normal limits, without dilatation, deformity, or displacement of the ventricular system. This paper is based on the author's personal experience with 61 cases, 15 of which were reported previously.

Only nine of the 61 patients gave a history of previous middle ear infection. In 23 patients the syndrome was preceded by infection elsewhere in the body or trauma to the head. Twenty-nine patients gave no history of preceding infection; of these, 18 were women.

The etiology of this condition is still unknown and probably variable. Those patients in whom the symptoms are preceded by infection of an ear or mastoid may well have mural thrombi in the superior longitudinal sinus or the major lateral sinus sufficient to interfere with cerebrospinal fluid absorption. To some extent this may also be true of the cases with preceding infection elsewhere than in the ear, or mastoid, or cerebral trauma.

In nearly half of the 61 cases, the syndrome was not preceded by infection or trauma. In these cases it occurred more frequently in females than in males and was more common in the middle decades of life than at other ages. The etiology under these circumstances may be of a toxic or allergic nature, and in women may be related in some manner to menstrual disturbances of electrolyte balance.

The treatment in all cases is aimed at relieving intracranial hypertension. In mild cases this can be done by limitation of fluid intake and promotion of water excretion alone. In cases with more severe papilledema, subtemporal decompression should be done first, followed by the above measures.

The prognosis in the majority of cases is excellent, although many months or even several years may be required for the condition to subside completely.

Because of the favorable outcome in most cases and the uncertainty as to the etiology, the designation "benign intracranial hypertension" suggested by Foley, especially for those cases not preceded by infection or trauma, seems a desirable one.

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■ What we have said of the various parts of the body considered from the posterior to the anterior surface, we can say also of the various parts of the body considered transversely. We have shown that the left side of the spinal cord is the conductor of sensitive impressions coming from the right side of the body, and vice versa. Let us now examine what takes place in the right posterior limb when we divide the left side of the spinal cord. We find that, after a division of a part of the left lateral column, there is no diminution of sensibility anywhere in the right limb; if the section is deeper, and involves a part of the gray matter, with the whole of the left lateral column, sensibility is diminished everywhere in the right posterior limb; if the section is still deeper, so that there remains only a very slight part of the central gray matter, or of the anterior column on the left side, sensibility is then much more diminished everywhere in the right posterior limb, and, as in the preceding case, the same degree of diminution exists in all the parts of this limb. At last, when the whole of the left side of the cord has been divided, there is only in the right limb the false appearance of sensibility which has been explained in the preceding lecture. It results from these facts, that the various parts of this limb, the outside parts, the inside parts, and the middle parts, are not represented in the left side of the spinal cord by conductors of sensitive impressions disposed in distinct layers; because, had it been so, the diminution of sensibility, instead of being gradual everywhere and appearing in all the parts at the same degree, would have taken place in one part more than in another, after some of the sections. It seems, therefore, that transversely as well as in the direction from behind forwards, the spinal cord, in the various parts of the conducting zone, contains fibres or other elements, conductors of sensitive impressions coming from the various parts of the body, one lateral half of the cord however, being the agent of transmission for the opposite lateral half of the body. We can say, also, that the sensitive impressions made on any point of a lateral half of the body are transmitted to the sensorium by conducting elements, distributed in all parts of the lateral half of the spinal cord on the opposite side.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System,* published in 1860.

Structural Spread of Cortically-Induced Epileptic Discharges

A. Earl Walker, M.D., Gian Franco Poggio, M.D. and Orlando J. Andy, M.D.

IN RECENT YEARS it has been assumed by physiologists that focal epileptic discharge involves subcortical structures in varying degrees, but a detailed analysis of the relationships has not been made. Usually it is inferred that the circuits are corticothalamic and thalamocortical, with other structures participating to lesser degrees.[1] However, neurologists have not been so impressed with the role of subcortical structures. In most clinical descriptions of epileptic discharge, it has been assumed that focal epilepsy spreads by involvement of contiguous cortex, with little, if any, mention made of the propagation of the discharge through the subcortical structures. During the past few years, our experience with multiple subcortical recordings both in experimental animals and man has forced upon us the view that the subcortical structures play a much more important role in the propagation of the epileptic discharge than has been considered in the past.[2] Indeed, the subcortical structures may be responsible for the initiation and continuation of what appears clinically to be a focal cortical epileptic attack.

The progressive involvement of subcortical structures as a cortically-induced seizure spreads from a small area of the motor cortex is well demonstrated in figure 1. In this record, in which the activity of various subcortical structures has been tapped by bipolar concentric electrodes at the same time that cortical activity is being recorded through silver ball electrodes, the first manifestations of the convulsive episode occur in the cortex with minimal involvement of the subcortical structures. However, as the attack becomes more extensive to involve the entire side, one notices that the subcortical structures participate to a much greater extent. It is noteworthy that the basal ganglia, which show minimal discharge with local twitching of the right shoulder, have rather marked spiking with twitching of the entire right side as well as the cerebellum, vermis, pontine reticular substance, dentate nucleus, and the hippocampus, all showing spiking. On the other hand, the discharge of the motor cortex is little, if any, more pronounced in the primarily involved areas, that is at electrodes 9,

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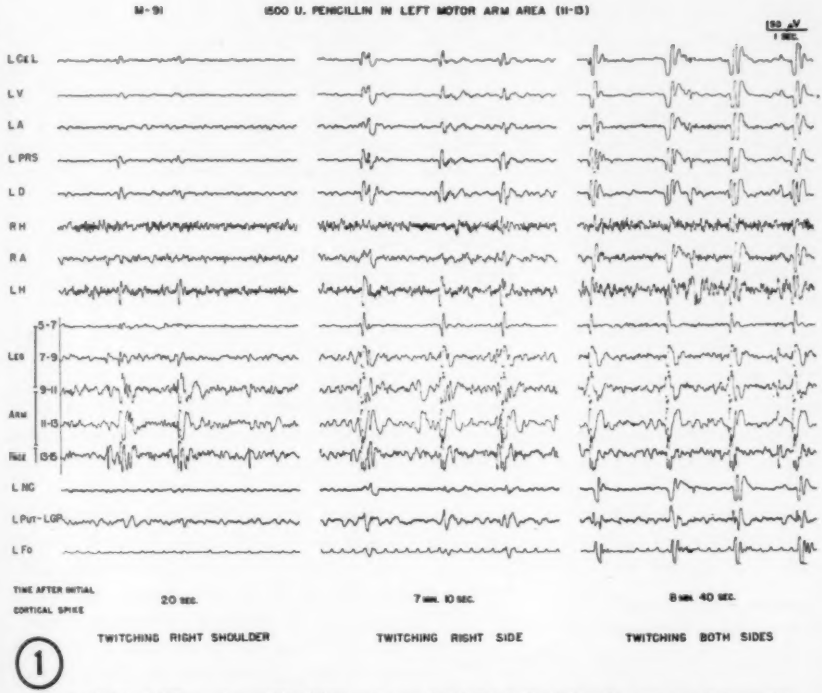

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FIG. 1. M-91. 1,500 u. of penicillin (0.01 cc.) were injected into the left motor arm area between the electrodes 11 and 13. Penicillin spikes appeared in the cortex four minutes after the injection. The section of the record taken at 20 seconds after the initial cortical spike shows the spread of the epileptic activity to adjacent cortical regions and the subcortical responses in the ipsilateral cerebellum (LCeL, LV, LD), reticular substance of the pons (LPRS), hippocampus (LH), and basal ganglia (LPut-LGP). At this time the clinical manifestations were twitching of the contralateral shoulder, synchronous with the cerebral discharges. Subsequently the twitching progressed to involve the entire contralateral side of the body; the middle tracing (taken seven minutes after the initial cortical spike) shows discharges present in the ipsilateral motor cortex and subcortical structures. When the twitching became generalized (tracing at right), all the cortical and subcortical regions sampled exhibited discharges of high amplitude. It is noteworthy that the progressive involvement is more evident in the subcortical than in the cortical regions. The seizure took much longer to spread from the initial site of twitching (right shoulder) to the entire side (seven minutes) than to extend from the one side to both sides of the body (1½ minutes).

The abbreviations used in the illustrations are as follows: A—amygdala, AC—anterior commissure, CC—corpus callosum, CF—calcarine fissure, CeL—cerebellar hemisphere, CG—cingulate gyrus, CL—nucleus centralis lateralis, CN—caudate nucleus, D—dentate nucleus, Fo—fornix, GP—globus pallidus, H—hippocampus, HG—hippocampal gyrus, HYP—posterior hypothalamus, IC—internal capsule, LP—nucleus lateralis posterior, MD—nucleus medialis dorsalis, PRS—pontomesencephalic reticular substance, Put—putamen, S—septum pellucidum, SB—nucleus subthalamicus, SN—substantia nigra, V—vermis of cerebellum, V Po—posterior vermis of cerebellum, Ve—ventricle, ZI—zona incerta. The letters R or L before an abbreviation indicate right or left.

11, 13, and 15, and has spread only slightly to electrodes 5 and 7. The right subcortical structures (hippocampus, amygdala) do not discharge in unison with the left ganglia. When the twitching becomes pronounced on both sides, the cortical activity is not increased, in fact there may be less cortical activity,

but the subcortical discharges are greatly augmented and present in the basal ganglia on both sides in all structures sampled. It then seems that generalization of the attack is associated with greater and more widespread involvement of the subcortical structures. One cannot conclude with certainty that this subcortical activity necessarily represents the only causative factor in the dissemination of the seizure. However, the correlation of progressive subcortical activity and clinical seizure has been consistently present in our experience. This, then, implies that the subcortical structures are playing a prominent role, not only in the development of the epileptic discharge, but in its maintenance and dissemination. In this paper we shall indicate the patterns of subcortical response to focal epileptic discharge induced in various cortical regions.*

GENERAL CONSIDERATIONS OF FOCAL EPILEPTIC DISCHARGE

It is well known that epileptic attacks beginning in the cerebral cortex are frequently characterized by initial phenomena which indicate the site of their origin. Seizures stemming from the frontal agranular cortex are often initiated by a sudden loss of consciousness or unconscious turning of the head and neck or trunk. Those attacks originating in the central gyri have focal twitching or jerking or paresthesias which may spread by Jacksonian march or by brisk extension to the entire half of the body, and subsequently become generalized. Epilepsies beginning in the occipital cortex are often associated with visual aurae. Seizures arising from the temporal cortex may have many varied and sometimes bizarre aurae, which are well known as psychomotor manifestations. Although the cortical electrical discharges may be essentially the same in all of these cerebral areas, the subcortical patterns of propagation are quite distinct. It is possible that the clinical manifestations of such seizures are more related to these lower mechanisms than to the purely cortical stimulation. This problem has been investigated in the monkey and the data presented in this paper are based upon research carried out on the macaque. Although some studies of the basal ganglia activity in man have been made, these are not sufficient in number to warrant a statement as to how closely the findings in man approximate those in the monkey.

PATTERNS OF PROPAGATION FROM THE CEREBRAL CORTEX

1. *Frontal granular cortex.* In the monkey, the cortex on the convexity of the frontal lobe anterior to the arcuate sulcus is generally considered a granular cytoarchitectonic type. This cortex extends onto the inferior and medial surface of the frontal lobe. Thus far only the granular cortex on the orbital surface and upper convexity of the frontal lobe has been investigated.

Adequate electrical excitation of this frontal granular cortex induces a local afterdischarge, with propagation to the opposite homologous frontal area in 80 per cent of stimulations. This firing of

*For details of the experimental technics, the reader is referred to the paper by Poggio, Walker, and Andy.[2] The stimulation used in most of the procedures was derived from a thyratron tube, the discharge of which had a time constant of 3 msec., and which was fired at a frequency of 30 per second for five seconds. In some experiments other technics of cortical excitation, such as the local application of penicillin or strychnine, were employed, with similar but sometimes more discrete patterns of propagation being demonstrated.

the contralateral frontal cortex occurs immediately after stimulation and persists as long as the primary afterdischarge. Other cortical areas might be involved: in approximately 50 per cent of cases the ipsilateral motor cortex is affected, the temporal pole much less frequently. In the ipsilateral caudate nucleus, paroxysmal discharges are seen in approximately 50 per cent of cases, and in the contralateral caudate nucleus in 25 per cent of cases. This subcortical activity in the caudate nucleus consists usually of low amplitude spikes synchronous with those in the cortex and, at times, slow waves or bursts of spikes and waves. It is noteworthy that many other subcortical structures are commonly involved, such as the amygdala, hippocampus, nucleus medialis dorsalis of the thalamus, cerebellum, and basal brainstem nuclei (figure 2).

2. *The central cortex.* The pattern of epileptic discharge from the pre- and postcentral gyri on the convexity of the brain appears to be more or less similar and may be discussed as a unit. Following excitation of a portion of the central

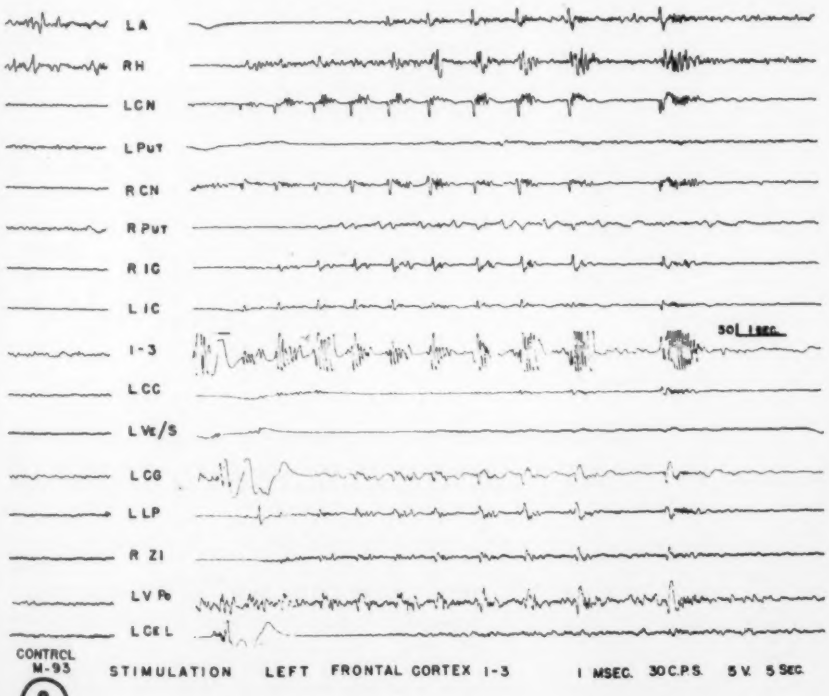

FIG. 2. M-93. Stimulation of the left prefrontal cortex (5 volts, 30 cps, 1 msec. pulse duration, for a period of 5 sec.). The record shows the resulting afterdischarge. It is interesting to note the widespread involvement of the subcortical structure but the absence of any response in the putamen of either side (6 hr. 23 min. after the beginning of the experiment, 66th stimulation).

cortex, an afterdischarge usually occurs in the contralateral homologous cortex (90 per cent of cases). Rarely the ipsilateral frontal cortex and the posterior parietal cortex become involved. Much more commonly, in fact in 95 per cent of cases, there is a concomitant firing in the ipsilateral putamen. Involvement of the ipsilateral thalamus, particularly of the lateral nuclear mass, occurs in about 30 per cent of stimulations. Ipsilateral brainstem nuclei, such as the subthalamic bodies, substantia nigra, pontine reticular substance, and others, may also be the site of afterdischarge. However, the caudate nucleus and the hypothalamus are usually not involved; in some cases the amygdala or hippocampus or both have fired in unison with the spiking of the motor cortex (20 per cent). It is noteworthy that the cerebellar hemispheres fire synchronously with the

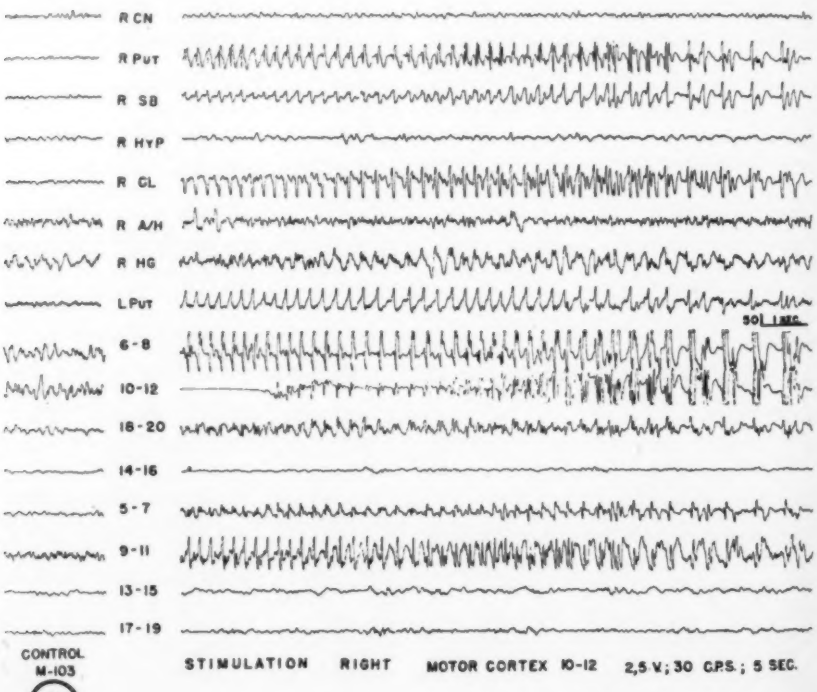

FIG. 3. M-103. Stimulation of the right face motor cortex with a thyratron stimulus of 2.5 volts, 30 cycles per sec. for 5 sec., induced afterdischarge at the point of stimulation (10-12), the adjacent face motor cortex (6-8), the contralateral face motor cortex (9-11), and to a lesser extent the more anterior cortex about the arcuate sulcus (5-7). Note that the posterior parietal (13-15) and occipital cortex (14-16 and 17-19) are not involved. The putamen on both sides and the right nucleus centralis lateralis, as well as the right subthalamic body, participate in the attack, but not the caudate nucleus, the hypothalamus, the amygdala, and hippocampus (8 hr. 52 min. after beginning of the experiment, 30th stimulation).

discharges of the contralateral motor cortex (figure 3).

3. *The temporal lobe.* Stimulation of the temporal convolutions, particularly the anterior portion of the temporal lobe, has consistently given rise to afterdischarge of the ipsilateral temporal cortex, the ipsilateral amygdala and hippocampus (85 per cent of cases), and frequently in the frontal granular cortex and face area of the motor cortex (approximately 50 per cent). With further propagation of the seizure, structures related to the hippocampus and amygdala (septum, cingulate gyrus, and hypothalamus) are progressively involved, or spread may be through the orbital frontal cortex to the caudate nucleus (10 per cent). Involvement of the contralateral amygdala and hippocampus occurred in one-third to one-half of the cases and of the contralateral temporal cortex in approximately 70 per cent of cases (figure 4).

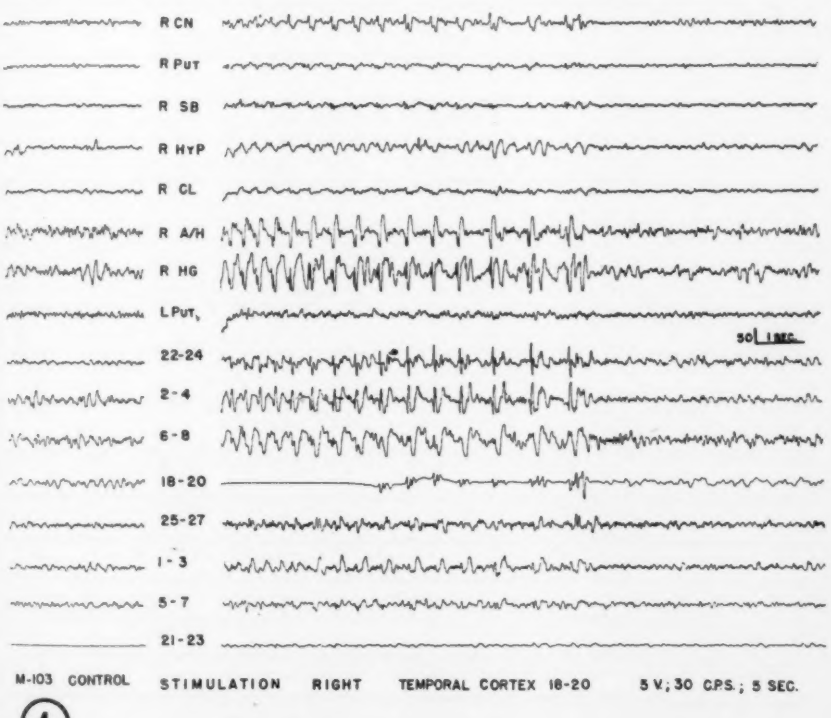

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FIG. 4. M-103. Stimulation of the right superior temporal gyrus below the face motor arm area (5 volts, 30 cps., for 5 sec.) induced afterdischarge at the site of stimulation (poorly shown in 18-20 due to amplifier block), in the prefrontal cortex (2-4), in the cortex along the posterior lip of the arcuate sulcus (6-8), and the orbital frontal cortex (22-24), as well as in the right hippocampus and amygdala and slightly in the right caudate nucleus. Note the absence of spiking in the putamen, brainstem, and thalamus (8 hr. 10 min. after beginning of experiment, 21st stimulation).

4. *The occipital cortex.* The pattern of propagation from the occipital cortex is more difficult to study than that from the other areas, because the response to electrical stimulation of the occipital cortex is usually confined locally without spread to other structures. Occasionally the parietal lobe and at times the temporal structures are implicated (figure 5).

DISCUSSION

The relatively consistent participation of certain nuclei in afterdischarge elicited from one cortical area lends support to the thesis that such ganglia are mutually related in the propagation of an epileptic discharge. That these structures constitute a circuit of any type cannot be stated from the evidence at hand. However, their constant participation would favor the suggestion that they form a functional complex or system in terms of epileptic activity. It is noteworthy that the basal ganglia are primary members of each of these systems

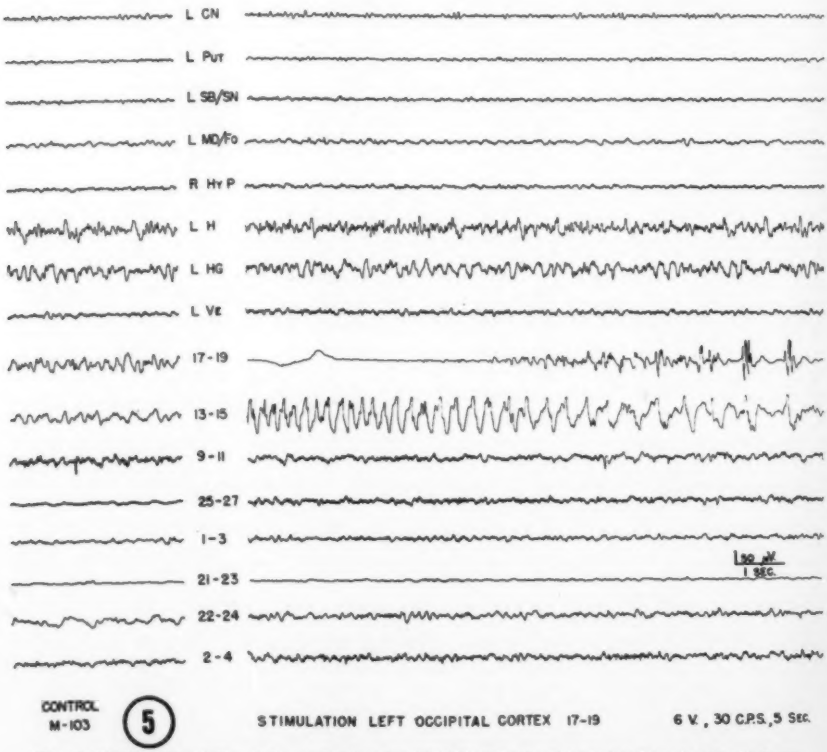

FIG. 5. M-103. Stimulation of the occipital cortex (17-19) (6 volts, 30 cps, for 5 sec.). Afterdischarge at the point of stimulation and in the posterior parietal cortex (13-15) lasts for about 10 sec., but no subcortical responses are recorded (11 hr. 18 min. after the beginning of the experiment. 48th stimulation).

and that the secondary members within the brainstem are less prominent.

Three such systems seem well defined.

1. The frontal granular cortex, the caudate nucleus, and the dorsomedial thalamic nucleus form a consistent interacting complex.

2. The central cortex, the putamen, and lateral nuclear mass of the thalamus form another closely related system.

3. The temporal cortex, the amygdala, hippocampus, and septal nuclei constitute a third functionally related group.

Although the cortex generally activates each of these systems, under certain conditions any one of the structures may fire the entire complex. This intraaction is best demonstrated in the temporo-amygdala-hippocampal system.

Although emphasis has been placed upon the individuality of the different systems of epileptic propagation, there is considerable interrelationship between them. For example, as the discharge

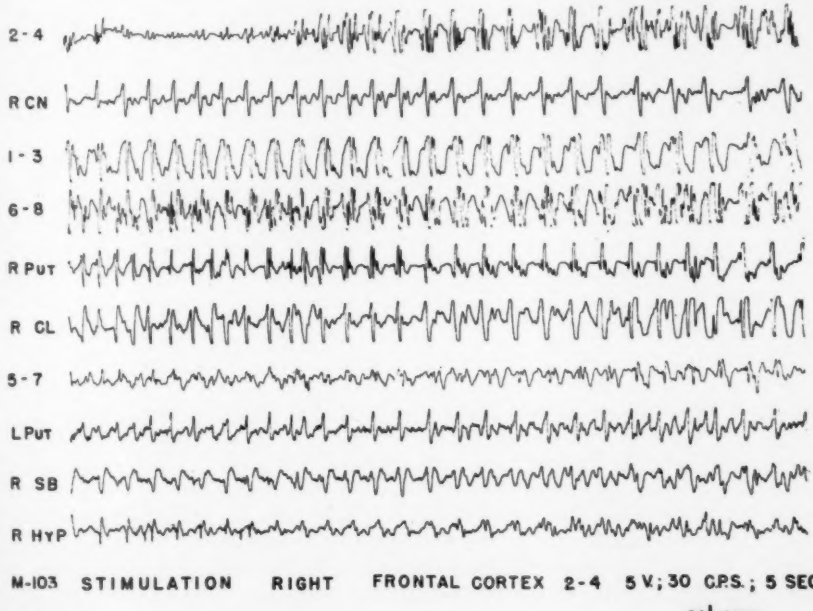

FIG. 6. M-103. Initial concomitant afterdischarge in two different systems with independent rhythm. Stimulation of the right frontal cortex (2-4) (5 volts, 30 cps, for 5 sec.) gives rise to an afterdischarge which involves the ipsilateral caudate nucleus and the contralateral homologous cortical areas (fronto-caudate-thalamic system). At the same time discharges are present in both ipsi- and contralateral centro-putamen-thalamic systems. The structures belonging to each system exhibit the same temporal pattern of discharges (intraaction), but each system has its own individual independent rhythm. It is interesting to note that activity in the right subthalamic nucleus is initially synchronous with the discharges in the fronto-caudate-thalamic system, but subsequently develops the rhythm of the centro-putamen-thalamic system. The subthalamic region may be activated at different times by both systems. (8 hr. 16 min. after the beginning of the experiment. 23rd stimulation).

from the centro-putamen-thalamic system is progressing, the temporo-amygdala-hippocampal system may begin to discharge either synchronously or asynchronously with the central system and continue after the latter has stopped its activity.

The interaction of these systems may develop at the beginning of the afterdischarge or some time thereafter. The initial concomitant afterdischarge in two systems may be due to primary direct stimulation of several systems as the result of an intense excitation, or may be due to the immediate anatomic spread from a complex such as the fronto-caudato-thalamic to subcortical structures intimately related to other systems. Usually but not always these initial concomitant seizures have synchronous discharges, but as the seizure progresses each system may take on an independent rhythm (figure 6).

The interaction of these systems may, on the contrary, develop over a shorter or longer period. This may occur within a second system as a progressive build-up which may be synchronous or asynchronous with the activity of the primary discharging system. Again the activity may develop in more and more subcortical nuclei having the same frequency of discharge as the primary focus. A third type of late interaction consists of the prolongation of afterdischarge in a second system following cessation of firing in the first, with possibly the tertiary involvement of another system which again may outlast the second. In any of these interactions the seizure may become generalized sooner or later. The third type of interaction is particularly prone to occur between the centro-putamen-thalamic and temporo-amygdala-hippocampal systems, but it may occur between any of the systems. For an unknown reason, in some animals the occipital cortex is prone to show this type of secondary involvement (figure 7). These interactions remain unilateral for long periods of time (minutes) and may never become bilateral or generalized.

The concomitant activity of these systems may break up simultaneously or seriatim. There may be a disappearance of the integration not only between individual systems but within one complex, so that the temporal cortex and amygdala may fire asynchronously toward the end of a seizure. In general in such cases, it is the cortex which drops out before the subcortical ganglia.

These studies of the pattern of propagation of an epileptic discharge may offer an explanation for certain clinical phenomena seen in focal cortical seizures. The characteristics of the frontal seizures are sudden bilateral cortical and subcortical spread, little intraactivation of the system, and minimal interactivation of other systems. Clinically, seizures arising in the frontal lobe present sudden loss of consciousness without focal motor phenomena. Are these characteristics to be equated? Or are they dependent upon some other as yet unrecognized factor? Central seizures give rise to unilateral subcortical activation, moderate intraactivation, and moderate interactivation of other systems. Clinically, seizures beginning in these gyri are characterized by focal motor or sensory phenomena, little impairment of consciousness, and late but usually abrupt generalization. Can these be correlated? Is the absence of widespread subcortical involvement to be associated with the preservation of consciousness and the tendency for interaction with

other systems to be considered the mechanism for generalization? Temporal lobe seizures have a pattern of extensive subcortical spread, little propensity to remain unilateral, and great likelihood to interactivate with other systems. Clinically, these seizures are characterized by some impairment of consciousness associated with bizarre behavioral disturbances without clear focal signs and moderate tendency to generalization of the attack. Are these correlated? Is the extensive subcortical spread related to the clouding of consciousness?

These are questions which cannot be answered positively at the present time.

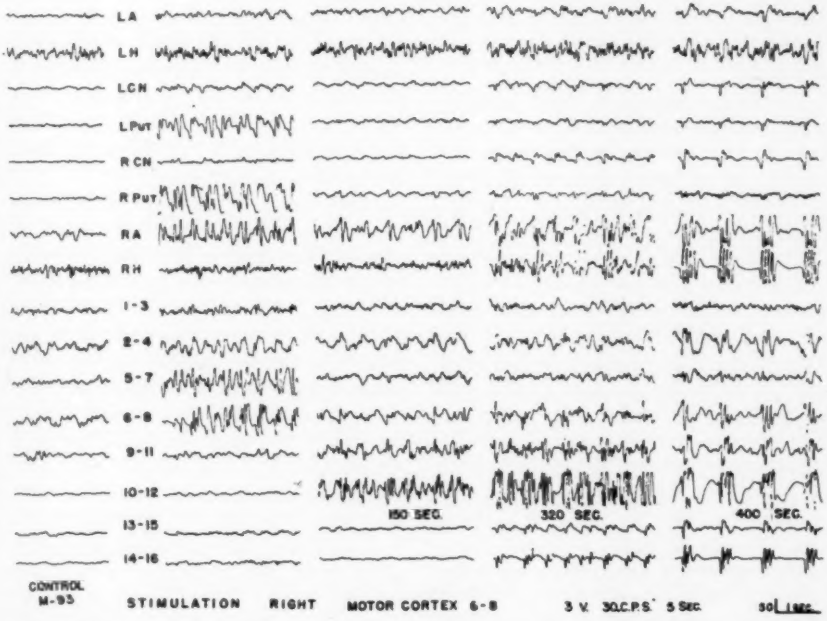

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FIG. 7. M-93. Late interaction between different cortico-subcortical systems. Immediately after stimulation of the right motor cortex (6-8), (3 volts, 30 cps., for 5 sec.), convulsive discharges are present in both motor cortices (6-8, 5-7), right and left putamens and right amygdala. After 2 min. 30 sec. the activity in the centro-putamen-thalamic system is greatly reduced in amplitude and frequency, but discharges are building up in the right occipital cortex; 2 min. 30 sec. later a consistent, high voltage convulsive activity is recorded from the right occipital cortex; synchronous discharges are present in the ipsilateral and contralateral temporal cortex (14-16, 13-15), in the ipsilateral hippocampus amygdala, and caudate. Some responses are recorded also from both the contralateral occipital and ipsilateral motor cortices. Subsequently (1 min. 20 sec. later) a well organized, widespread synchronous epileptic activity can be recorded from all the structures sampled on the right side, and from the left caudate nucleus, occipital cortex, and to a lesser degree in the temporal and motor cortices and putamen. The seizure continues 3 seconds more and eventually ends abruptly in all the sampled structures. The second portion of the tracing (150 sec.) leads us to suspect that the right amygdala played a prominent role in the interactions of these systems in this case. This is the type of attack "will o'-the-wisp" which Walker and Johnson[5] described.

Other investigators have concluded that the explanation lies in some other mechanism, such as the centrencephalic system postulated by Penfield,[3] the thalamocortical sectors suggested by Gastaut,[1] and the diffuse involvement of the cortical association areas, proposed by Andy and Akert.[4] Irrespective of the final solution, it must take into account the spread of the epileptic discharges throughout the subcortical grey masses.

SUMMARY

So-called cortical epileptic seizures, when studied with depth electrodes, are seen to be accompanied by marked involvement of many subcortical structures, depending upon the site of origin of the cortical discharge. The afterdischarge from frontal, central, temporal, and occipital cortices spreads to different subcortical nuclei. Three main structural patterns of propagation may be distinguished: 1) from the frontal granular cortex to the caudate nucleus and to the contralateral frontal granular cortex and subsequently to many other subcortical structures, 2) from the central cortex to the ipsilateral putamen and thalamus and to the contralateral homologous central cortex, and 3) from the temporal cortex to the amygdaloid hippocampus complex and its subcortical projection sites, namely the septum, hypothalamus, and medial thalamic areas. Other subcortical nuclei participate in focal attacks much less consistently but may become involved in generalized seizures. The generalization of a convulsive seizure is usually associated with propagation of the discharge from one system to another.

This concept of epileptic propagation through subcortical structures offers a possible explanation for many of the clinical phenomena seen in various types of seizure. Moreover, it introduces a mechanism whereby subcortical structures may be the primary site of what would appear to be a cortically-induced epileptic discharge.

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Hyperinsulin Neuronopathy

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and Edward H. Lambert, M.D.

PROGRESSIVE MUSCULAR ATROPHY is a disease of the motor systems occurring in adult life, which is invariably fatal and for which there is as yet no known therapy. The differentiation and recognition of muscular atrophy, the etiology of which is known and for which there is therapy, are therefore of clinical and of theoretic importance. Such a progressive muscular atrophy has been reported as a complication of hyperfunctioning tumors of the islets of Langerhans.[1-3]

In this communication we will review the history and findings in 20 patients with muscular atrophy secondary to hyperinsulinism. One of these patients was seen and examined by us recently. Nine additional patients were examined by our colleagues during the years 1927 through 1953 because of complaints of muscular weakness or paresthesias or both associated with hyperinsulinism. There has been a previous report of the clinical aspects of the latter group of patients.[4] An additional ten patients previously described in the world literature are included in this review.

REPORTS FROM THE LITERATURE

Case 1. Laroche and associates[5] in 1928 described a 35 year old woman who had had spontaneous hypoglycemic episodes since 1924. These were so severe and frequent that the patient awakened herself at midnight and again at 4:00 a.m. to take food and thus avoid an attack. During a severe attack in August 1927, the patient was in coma for several days. Later she noted localized tingling in the hands and forearms and clumsiness and weakness of hands and feet.

Neurologic examination revealed a weakness of the finger flexors. The muscles of the trunk were not involved, and she was able to move the hip and knee joints well. The patellar reflexes were present, although the Achilles reflex was very weak on the right and absent on the left. No objective sensory findings were noted.

The authors concluded that this patient's "polyneuritis" was caused by the prolonged hypoglycemia she had had in August 1927.

Case 2. Blau and associates[6] reported in 1936 on a 49 year old man with hyperinsulinism who had far-advanced degenerative changes of the central nervous system secondary to hypoglycemia. This patient also had peripheral muscular weakness and sensory hypesthesia in a stocking-and-glove distribution. These findings were thought to be indicative of peripheral neuritis.

Cases 3 and 4. Two similar patients with pancreatic adenoma were reported by Silfversklöld.[7] The first, a 34 year old man with confirmed hyperinsulinism, complained that his hand muscles had become atrophic and useless for fine movements. An electromyogram revealed signs of a neurogenic atrophy of the hand muscles and of the tibialis anterior muscle. Histologic examination of the thenar muscle in this patient demonstrated no change in the muscle fibers suggestive of muscular dystrophy.

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The second patient described by Silfversklöld[7] was a 17 year old youth with confirmed hyperinsulinism. The neurologic examination revealed a foot drop and weakness of the hands with no obvious atrophy. The right ankle jerk was absent; the left was reduced.

Case 5. Lidz and associates[8] in 1949 reported on a 23 year old man in whom long-standing hyperinsulinism due to an islet cell adenoma of the pancreas was accompanied by widespread damage to the central nervous system, including abnormalities resembling progressive muscular atrophy. They reported that all of the manifestations of this illness, except for the residual muscular atrophy, disappeared after removal of the tumor. Examination of this patient revealed that the small muscles of his hands were symmetrically wasted and flexion and extension of the wrists were very weak, while abduction and adduction of the fingers were absent. The muscles of the upper arm were moderately strong. The muscles of the calves were small, plantar flexion of the foot was very weak, and dorsiflexion was impossible. No fasciculations were observed, and the results of sensory examination were negative. The deep reflexes were normal except for the absence of the ankle reflexes.

Case 6. Levrat and Brette[9] reported in July 1948 on a 31 year old woman who, within the last months of the course of her illness, was proved to have hyperinsulinism. During this period severe muscular pain and weakness developed, which they attributed to a degenerative myositis secondary to a dysfunction of glycogen metabolism. Pathologic examination revealed that she was suffering from a low-grade carcinoma of the islets of Langerhans.

Case 7. Willner and Weinstein[10] reported in 1950 the history of a 49 year old woman with hyperinsulinism in whom, during the course of her illness, weakness and numbness developed in both legs, feet, and fingers. A neurologic examination revealed that all of the deep reflexes other than the biceps reflex were absent. The Babinski signs were positive bilaterally. Position sense was slightly impaired in the toes but not in the hands. A pancreatic islet cell adenoma was found at operation and removed. After operation the clinical signs and symptoms, other than the neurologic ones, cleared rapidly.

Case 8. Tom and Richardson[3] reported the findings in a 33 year old woman with an islet cell adenoma of the pancreas in whom, after a nine-month history of episodic hyperinsulinism, severe and fatal encephalopathy and myelopathy developed. At necropsy, histologic sections of the spinal cord disclosed widespread degenerative changes in the ventral horn cells as the cause of the paralysis and wasting of distal limb muscles which the patient had exhibited clinically. Although they did not obtain an abnormally low blood sugar during life, they stated that the pathologic findings of a benign islet cell pancreatic tumor and the nature of the severe cerebral changes clearly established the diagnosis.

Case 9. In 1953 Barris[1] reported the findings in a 42 year old man with progressive weakness and wasting of his muscles. The patient had had episodic confusional states, during one of which a fasting blood sugar of 30 mg. per 100 cc. was reported. Examination revealed diffuse atrophy of moderate degree of the appendicular and truncal musculature, generalized muscle fasciculations, and increased myotatic irritability. An electromyographic examination revealed fibrillation potentials in the affected muscles. The patient's gait was of a steppage type, his hand grips were weak, and he had difficulty in rising to a standing position. The muscle stretch reflexes were intact and hyperactive, except for the Achilles reflexes which were diminished. There were no sensory abnormalities. Four months after onset of the patient's illness, a pancreatic adenoma was removed. Seven months after removal of the tumor, the patient was able to walk and was reported improved.

Case 10. Trethowan[11] reported the findings in a 49 year old woman with hypoglycemia, from whom an adenoma of the pancreas was removed in 1955. After an acute episode of hypoglycemia, distal paresthesia and muscle weakness developed. Examination some months after removal of the adenoma revealed no muscle abnormality, although the paresthesia persisted and stereognosis and two-point tactile sensation were diminished in the patient's hands.

OUR MATERIAL

Case 11. A 28 year old unmarried woman, a physical education teacher, was first seen at the Mayo Clinic on February 10, 1955. She and her family physician reported that she had had episodic periods of confusion for the previous six months, and for three months prior to her exam-

ination at the clinic she had had episodes of coma. During one such episode it was reported that her blood sugar had fallen to 26 mg. per 100 cc. In the two weeks prior to her admission to the clinic, she had observed paresthesias in her hands and feet.

Examination revealed the patient to be mentally dull but oriented as to time and place. The muscle stretch reflexes were hyperactive bilaterally in the upper extremities and normal in the lower extremities. No abnormal reflexes were elicited. Examination of the musculature revealed weakness in the distal portions of all four extremities. There was atrophy of the thenar and interosseous muscles, and an occasional fasciculation was noted in these muscles. Weakness was also noted in the anterior tibial muscles bilaterally. The peripheral nerves were not tender to palpation. Superficial and deep sensation were objectively normal.

Further observation and laboratory studies revealed that the patient had episodes in which the blood sugar fell to less than 40 mg. per 100 cc. and during these episodes she became confused and sometimes comatose. At these times intravenous administration of glucose caused prompt recovery. A spinal fluid examination revealed normal manometric pressures, 70 mg. of protein per 100 cc., 53 mg. of sugar per 100 cc., 710 mg. of chloride per 100 cc., and a negative Kolmer reaction.

Electromyographic examination revealed grade 2 to 3 fibrillation in the left forearm, hand, and leg muscles. No fasciculations were observed. The motor unit potentials as observed in the electromyogram were greatly reduced in number, but were of normal size and fired at a rapid rate during strong effort to contract the muscle. Conduction studies of the left ulnar nerve revealed that the response of the left hypothenar muscle to stimulation was approximately 5 per cent of normal. Conduction velocity of the functioning nerve fibers was normal. The strength-duration curve of the hypothenar muscle was typical of partial denervation.

It was also determined that the patient was suffering from hypercalcemia. Operative exploration of the parathyroid glands revealed multiple parathyroid adenomas, and all but a portion of the right superior gland was removed on February 26, 1955. An exploratory laparotomy revealed multiple adenomas of the pancreas, and subtotal pancreatectomy was performed on March 11, 1955. On June 2, 1955 most of the remainder of the patient's pancreas was removed because of a recurrence of hypoglycemia.

The patient's clinical symptoms of recurrent coma and confusion improved after the initial pancreatectomy. Similarly, the paresthesias and weakness in her hands and feet also improved. A biopsy of the sternocleidomastoid muscle on February 26, 1955 revealed no abnormalities. A biopsy of the left gastrocnemius muscle taken immediately after the subtotal pancreatectomy revealed that the majority of muscle fibers were normal. However, there were scattered fibers which took a more basophilic stain and contained centrally placed large nuclei with prominent nucleoli. These fibers were present particularly along the tendinous junction. Around some blood vessels in the fascia were collections of small round cells. There was a similar focal area in one muscle fascicle. The picture was not that commonly seen in polymyositis but did indicate some degenerative changes in the muscle fibers.

In July 1955 examination revealed that the patient had shown clinical improvement, and, although her hands were still weak, the paresthesias had disappeared. In January 1956 the patient wrote that she was using insulin for the surgically induced diabetes. She was also taking pancreatin to aid digestion of food. Her appetite had increased and she was gaining weight. She was now able to walk without crutches and was trying to run again.

Case 12. A 44 year old white man first noted episodic mental dullness and confusion in the morning and before delayed meals in 1934. In 1940 examination during such an episode revealed a blood sugar of 35 mg. per 100 cc. Early in 1940 he had noted the onset of paresthesias in his hands and feet, and in December he had noted atrophy and weakness in both hands and feet. A pancreatic adenoma was removed in December 1940 and the hypoglycemic episodes were completely relieved. A diagnosis of pernicious anemia was also made at this time. Repeated examinations were made in 1941, 1943, and 1946, at which time the patient continued to complain of weakness in the hands and feet. This was most pronounced in the intrinsic muscles of the hands and in the muscles of the lower legs. No pyramidal tract signs were observed, and, although the patient continued to have paresthesias, no sensory abnormalities could

be elicited. The deep tendon reflexes were active and equal except for absent Achilles reflexes. Fasciculations were observed in the hand muscles. In response to a recent inquiry, the patient has reported that the weakness in his hands has persisted, although he is still able to work and write in spite of this weakness.

Case 13. A 48 year old white man reported that he had his first episode of unconsciousness with clonic and tonic movements in 1934. Following this initial episode, he had repeated convulsive attacks. In January 1935 he complained of his hands being numb after such an episode. He was examined at the clinic in March 1936, at which time it was observed that his general health was good. He remarked that his hands and feet felt numb and that he had trouble controlling them. Neurologic examination revealed some weakness in both hands and feet, with an inability to hop on either foot. There was a minimal loss of pain sensation over the hands and feet. The deep reflexes were active and equal. During a convulsive episode a fasting blood sugar of 38 mg. per 100 cc. was obtained. The patient showed prompt improvement of symptoms after intravenous administration of glucose. Surgical exploration of the abdomen revealed a pancreatic adenoma, which was removed. In reply to a recent inquiry, the patient reported that he still had difficulty with weakness and numbness in his hands, but that the remainder of his symptoms had disappeared.

Case 14. A 55 year old white man reported that his symptoms began in May 1953 with an episode of confusion. After this he had many episodes, always relieved by orange juice or whisky. During an observed attack his blood sugar was reported as 35 mg. per 100 cc. The episode rapidly cleared after he drank some orange juice. The patient complained of numbness in the finger tips, with some soreness in the gastrocnemius muscle. He could not use his fingers as well as formerly and had weakness in the intrinsic muscles of both hands with minimal diminution of vibratory sensation over the finger tips. His deep reflexes were active and equal, except for the Achilles reflexes which were diminished. Abdominal exploration revealed an islet cell adenoma of the pancreas, which was surgically removed. In reply to a recent inquiry, the patient reported that he still has some weakness and numbness in his hands, although there has been no further progression of symptoms.

Case 15. A 25 year old married woman had had episodes of unconsciousness and drowsiness for three years prior to her admission to the clinic in July 1948. These attacks could be aborted by eating. During an attack her blood sugar was reported as 32 mg. per 100 cc., and the symptoms cleared rapidly on intravenous administration of glucose. A neurologic examination revealed weakness and atrophy of the intrinsic muscles of both hands. All other muscles seemed normal. No fasciculations were observed. The deep reflexes were hyperactive, and there were no pathologic reflexes. There was no pain or paresthesia, and no sensory abnormalities could be elicited. Roentgenograms of the cervical segment of the spinal column were negative. An islet cell adenoma of the head of the pancreas was removed surgically in July 1948, and the diagnosis was confirmed histologically. She reported recently that she regarded herself as well, although she still had weakness and atrophy of her hands.

Case 16. A 38 year old man described three episodes of bizarre behavior in the ten days prior to admission to the clinic in October 1946. Examination on that date revealed profound weakness in the hands associated with tingling in the tips of the fingers. During an episode of drowsiness and disorientation, his blood sugar was found to be 32 mg. per 100 cc. Prompt and dramatic recovery followed intravenous injection of 40 cc. of 50 per cent glucose. Neurologic examination revealed an isolated weakness of the flexor muscles of the fingers and wrist, the small muscles of the hands, and the biceps. The deep reflexes were within normal limits, and no abnormalities of the sensory system could be elicited.

Surgical exploration on November 12, 1946 revealed an adenoma in the midportion of the pancreas. This was classified as a grade 1 adenocarcinoma. The patient died November 21, 1946 of acute pancreatitis with fat necrosis and peritonitis of the lesser sac.

Case 17. A married woman was first seen at the clinic on October 29, 1941. She stated that her difficulty had begun in July 1941 when she had experienced episodes of confusion and apparently had had a convulsion. She reported that food would prevent an attack. Neurologic examination at the time of her admission to the clinic revealed some weakness of the pectoral muscles, the deltoids, and the latissimus dorsi bilaterally,

and less weakness in the remainder of the upper extremities. There also was minimal weakness observed in the psoas and quadriceps bilaterally. The reflexes in the upper extremities seemed to be diminished, while those in the lower extremities seemed essentially within normal limits. At the time of her admission, the patient complained of paresthesia of the hands and weakness of the shoulder muscles. Surgical exploration of the abdomen on December 1, 1941 was negative. She died on December 3, 1941 and necropsy revealed an islet cell adenoma of the pancreas.

Case 18. A 60 year old man had had a history of hypoglycemic attacks since 1936. He described tingling and burning of his hands and feet since September 1942. A pancreatic islet cell adenoma was removed on October 7, 1942.

Case 19. A 47 year old man reported that he had had episodic hypoglycemic attacks since 1948. He had had transient numbness of his fingers and toes since 1949. The results of neurologic examination were essentially negative. A pancreatic islet cell adenoma was removed in January 1950.

Case 20. A 47 year old married woman reported that she had noted the onset of numbness and tingling at the beginning of her episodic hypoglycemia. She had an islet cell tumor removed in January 1949.

COMMENT

In these 20 patients distal muscular atrophy or paresthesias or both occurred following severe and prolonged hypoglycemia. Hyperfunctioning adenomas of the islet cells of the pancreas were demonstrated as the cause of the hyperinsulinism in 18 patients. In two of these patients no pathologic changes in the pancreas were reported. In the case reported by Laroche and associates,[5] surgical exploration was not performed nor was there a report of pathologic findings. In the case reported by Blau and associates,[6] surgical exploration was performed and no abnormalities of the pancreas were observed. In the remainder of these patients solitary adenomas of the islet cells were found in 15 patients; in one patient multiple adenomas of the pancreas were observed, and in two additional patients low-grade malignant tumors of the islet cells were found. Nine of the ten cases included in our series have previously been described by Breidahl and associates[4] in a review of the "Clinical Aspects of Hyperinsulinism."

These symptoms of distal muscular atrophy and paresthesias usually began after severe episodes of hypoglycemia, and the patients were frequently comatose prior to the onset of their paresthesias and weakness. Because of the more dramatic nature of the cerebral symptoms of hypoglycemia, these peripheral manifestations were often ignored initially by both the physician and the patient. Unlike the other symptoms, however, the muscle atrophy did not clear following removal of the adenoma and tended to persist for months and even years after the hyperinsulinism had been cured.

Paresthesias were the usual earliest symptom of this syndrome. Fourteen of the patients in this series noted peripheral tingling or burning as their earliest complaint. It would seem probable that this symptom was not described more frequently in the patients reported in the literature because of the severity of the cerebral findings, which either prevented the reporting of this symptom or made the symptom appear unimportant. Paresthesias were the only symptoms in three of our patients, in whom we may assume that the pancreatic adenoma was removed before muscle weakness developed.

Objective evidence of sensory impairment occurred infrequently and was re-

ported in only five of these patients. Usually this consisted of diminution of two-point and vibratory sensation over the toes and fingers. In two patients there was a stocking-and-glove anesthesia late in the course of illness.

The syndrome of muscular weakness and atrophy was present in 17 of these patients. It usually began in the distal portion of the extremities either concurrently with the paresthesias or after the onset of the latter symptom. The muscular weakness was demonstrated on examination of the individual muscles and was further evidenced by a slapping gait and difficulty in performing fine movements with the hands, such as writing and eating. In some patients the weakness progressed to involve the truncal musculature, and the patient became bedfast. In one patient the weakness was limited to the hands, and in two other patients the weakness was most prominent in the limb girdles. One of the latter patients had an adenocarcinoma of the pancreas.[9]

The deep reflexes were characteristically reported as hyperactive except for the Achilles reflexes, which were diminished or absent. In this series the ankle reflexes alone were reported diminished in 11 patients, and additional reflexes were diminished in three other patients.

Muscle fasciculations were observed in the patient whom Barris[1] described and in one of our patients. In the former patient these fasciculations were widespread and were accompanied by marked muscle weakness. In the four patients in whom electromyographic studies were obtained, fibrillation potentials were observed in all affected musculature.

Removal of the pancreatic adenoma was reported by Barris,[1] Trethowan,[11] Lidz and associates,[8] Willner and Weinstein,[10] and by Silfversklöld[7] as arresting the progression of the muscular atrophy in their patients. Barris[1] reported that his patient demonstrated progressive improvement in strength for a five-month period following the removal of the pancreatic adenoma. Four of our seven patients with muscular atrophy are still living, and in response to a recent inquiry they all reported that there had been no progression of atrophy since removal of the pancreatic adenoma, although in each instance some atrophy and weakness were still present.

Various factors have been suggested as the cause of the distal muscle weakness and paresthesias. In several of our patients complicating illnesses occurred, which might have accounted for neuromuscular disorders. One of these patients had multiple adenomas of the endocrine glands[12] with hyperparathyroidism. Vicale[13] has described diffuse muscular wasting with severe bone pain in patients with hyperparathyroidism. This syndrome seemed enough unlike the specific distal muscular atrophy observed in our patient to make it unlikely that hyperparathyroidism was an important etiologic factorin his muscular atrophy.

The second patient in our series (case 12) had pernicious anemia in addition to hyperinsulinism. Although the paresthesias that he described might be related to the latter illness, he had no evidence of posterolateral sclerosis, which is the common neurologic complication of pernicious anemia. Moreover, the onset of muscular atrophy and paresthesias coincided with the onset of hyperinsulinism, and his symptoms improved following removal of his pancreatic adenoma.

Adams, Denny-Brown, and Pearson[14]

have suggested that the muscular weakness in the patient described by Levrat and Brette[9] was due to a myositis associated with carcinomatosis, since the adenoma of the pancreas was malignant in the latter case. A similar syndrome of limb-girdle weakness occurred in one of our patients who had a nonmalignant hyperfunctioning adenoma of the pancreas. In the one patient in our series with an adenocarcinoma of the pancreas, the clinical syndrome of distal muscular atrophy and weakness appeared similar to the symptoms observed in the remainder of our patients. Of the 91 patients with hyperinsulinism reviewed by Breidahl and associates,[4] 30 had malignant islet cell tumors. In only one of these cases were distal muscular atrophy and paresthesias described, although eight patients with this syndrome were observed in the 46 patients with nonmalignant hyperfunctioning adenoma of the pancreas. Thus, it would seem that there is no close correlation between the presence of this type of muscular weakness and carcinomatosis.

The occurrence of distal muscular atrophy and paresthesias following the injection of excessive amounts of insulin has been reported.[15] Ziegler[16] has recently reported that, following insulin coma therapy, paresthesias occurred in 13 of 22 patients and two of these patients had objective weakness in the small muscles of the hands. Baker[17] had similarly reported on a patient who, following insulin coma, described muscular weakness and paresthesias in the hands and feet. Thus, it would seem that severe episodes of hypoglycemia may be responsible for this syndrome, whether they be due to a hyperfunctioning adenoma of the pancreas or to injection of excessive amounts of insulin.

In the patients included in this report the distal muscular atrophies and paresthesias seemed directly related to hyperinsulinism. These symptoms and findings began during severe episodes of hypoglycemia, the presence of hyperfunctioning adenoma of the pancreas caused progression of these symptoms, and the removal of the adenoma arrested the progress of the atrophy and paresthesias. In a few patients a partial return of function occurred following removal of the adenoma.

The exact site of the lesions responsible for these symptoms has been controversial. Most authors agree that the symptoms are directly related to hyperinsulinism. Levrat and Brette[9] ascribed the muscular weakness in their patient to a myositis and compared their findings with the pathologic changes in the skeletal muscles of rabbits produced by repeated injections of insulin in shock doses. They postulated that carbohydrate is essential to the metabolism of the muscles and that prolonged hypoglycemia may damage the muscle fibers.

Barris[1] and others have described this syndrome as a progressive muscular atrophy, secondary to anterior horn cell disease. Moersch and Kernohan[18] reported that histologic sections of the spinal cord of a patient who had died of hyperinsulinism revealed dissolution of the anterior horn cells. Pathologic studies of the case reported by Tom and Richardson[3] revealed similar changes. Experimentally, Winkelman and Moore[19] have demonstrated that cats given large doses of insulin suffer loss of cells in the anterior horn and dorsal ganglia of the spinal cord.

Laroche and associates[5] originally re-

ported this syndrome as a peripheral neuritis. Clinically, the symptoms of paresthesias, pain, the occasional objective sensory changes, diminished reflexes, and the distal atrophy suggest an involvement of the peripheral nerves. In one patient whom we were able to study electromyographically early in the course of her illness, the nerve conduction times were normal, although the response of the left hypothenar muscle to stimulation was approximately 5 per cent of normal. The motor unit potentials were greatly reduced in number, but were of normal size and fired at a rapid rate. These findings are, in our experience, compatible with an early peripheral neuritis or anterior horn cell disease.

We would postulate that the pathophysiology of this syndrome involves both the anterior horn cells and the peripheral nerves, although pathologic evidence for the latter lesion is not available as yet. The presence of lesions involving both the anterior horn cells and the peripheral nerves is perhaps best described as a neuronopathy. We would, therefore, suggest that for the present this symptom complex might best be described as a "hyperinsulin neuronopathy."

The differentiation of this syndrome from progressive muscular atrophy can be made clinically and is seldom a difficult one. The dramatic character of the cerebral symptoms of hyperinsulinism usually so overshadows these peripheral findings that the latter are ignored. In our experience the cerebral symptoms have always antedated the neuronopathy. The history and findings of paresthesias, sensory hypesthesias, the absence of reflexes, and the distal location of the atrophy in hyperinsulin neuronopathy are sufficient to differentiate it from motor system disease. Peroneal muscular atrophy may simulate these findings. However, the absence of hypoglycemic crisis and the positive family history in the latter disease will aid in the differentiation.

In patients with chronic neuritis of undetermined origin the possibility of hyperinsulinism should be considered. In adults the presence of other symptoms of hyperinsulinism at the onset of the neuronopathy will aid in the diagnosis.

The neuropathies occurring in diabetes are a common and serious problem, which in some instances seems related to poor control of the diabetes with resultant frequent hypoglycemic crises. It would thus seem important to investigate in these patients the possibility that the diabetic neuropathy may be related to hyperinsulinism rather than hyperglycemia. The neuronopathy due to hyperinsulinism may be differentiated from diabetic neuropathy by the preponderance of motor findings and accentuation of symptoms by hyperinsulin crises.

CONCLUSIONS

A syndrome of distal muscular atrophy and paresthesias associated with hyperinsulinism has been observed in 20 patients. The symptoms and findings in this syndrome are reviewed, and it is suggested that this syndrome is best described as "hyperinsulin neuronopathy." The differentiation of this syndrome from progressive muscular atrophy, peroneal muscular atrophy, and chronic neuronitis is discussed. It is suggested that hyperinsulin neuronopathy may account for some of the neuropathies seen in diabetic patients.

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■ We think, and for many years already we have tried to prove, that the nerve-fibres employed in the transmission of each of the following sensitive impressions are as distinct one from the other as they all are from the nerve-fibres employed in the transmission of the orders of the will to muscles. We have not time enough to give the reasons we have for adopting this view: we will merely state that of the three hypotheses that may be made to explain a loss of one or of a few only of the following sensations, there is but one which agrees with the facts at present known; and we repeat that this one is, that the conductors of the various sensitive impressions are distinct one from another. The kinds of sensitive impressions which have different conductors are those giving the sensations of touch, tickling, pain, heat and cold, and the peculiar sensation which accompanies muscular contraction.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System,* published in 1860.

Study of the Early Changes Occurring in Degenerating Myelin

M. Wolman, M.D.

IT HAS BEEN POINTED OUT elsewhere[1] that the results of chemical studies of the changes occurring in myelin lipids during demyelinization cannot explain the fact that clear differentiation between normal and degenerating myelin can be obtained by a histologic staining method, the Marchi procedure and its modifications. Search for types of compounds which might be incriminated in the differential staining of degenerating myelin pointed toward the possibility that a heparin-like compound might be rendered available for reaction during the early stages of demyelinization.[1]

It is the purpose of this paper to report on experiments done on degenerating myelin by histologic and histochemical means, in order to determine whether carbohydrates are released during the early stages of demyelinization.

MATERIAL AND METHODS

Young albino rats of both sexes, 80 to 120 gm. in weight, were used. After shaving of the skin, the right sciatic nerve was cut in the gluteal region under ether anesthesia and the tip of the distal segment was freed for about 3 to 4 mm. and folded laterally. After closure of the skin, a narrow scalpel was introduced through the upper portion of the right orbit into the cranial cavity and moved to cut through the right frontal lobe. No antiseptic precautions were taken during the operations.

Groups of three rats were killed at intervals of one, two, three, four, six, eight, 12, 16, 20, and 30 days after operation. Left sciatic nerves and left cerebral hemispheres of the same rats served as controls to the right ones. The appropriate pieces of tissue were fixed for two days in 10 per cent formalin, rinsed in water, and embedded in carbowax according to a previously described procedure.[2] Sections were cut at 8 microns and picked from water onto albuminized slides.

The staining procedures used on the whole series of sections included: 1) direct staining of the sections with 1 per cent osmium tetroxide for one and seven days, and also with Marchi's, Busch's, and Swank-Davenport's solutions;[3] 2) the same procedures were applied also to sections which had been treated by potassium dichromate for seven days; 3) PAS staining both with aqueous and alcoholic periodic acid oxidations;[4] 4)

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permanganate-Schiff staining done by immersing the sections for one hour in 1 per cent potassium permanganate and then in Schiff's leucofuchsin; 5) colloidal iron staining according to Rinehart's procedure;[5] and 6) metachromatic staining according to Feyrter's "Einschlussfärbung."[6]

RESULTS

Staining by osmium tetroxide mixtures. Staining of the sections by osmium tetroxide and osmium tetroxide-oxidant mixtures as well as staining by the same reagents after dichromate treatment yielded results comparable to those reported in the literature. It should be noted, however, that in these experiments thin sections and not 2 to 3 mm. thick tissue blocks were exposed to the action of the reagents. It has been found that no differentiation between normal and degenerating myelin was possible in the sections treated by osmium tetroxide alone. Dark staining of degenerating myelin, from the eighth to twelfth day of degeneration, was obtained in prechromated sections treated by Marchi's mixture and in chromated and nonchromated sections treated by Busch's and Swank-Davenport's mixtures. The staining of degenerating myelin seemed to be at its peak around the sixteenth day, after which it became progressively weaker. The dark staining of degenerating myelin, although easily visible, was less intense than that obtained when the usual procedures are adopted, that is, when the staining was done in tissue blocks.

Staining by periodate and permanganate-Schiff technics. In all of these procedures from the day after operation degenerated myelin stained more intensely than normal myelin. The intensive staining was at first diffuse, but became progressively granular. Soon granules of intensely staining material were noted in the microglial cells surrounding the damaged area in the brain and in the Schwann cells of the nerve. By the sixteenth day the degenerating myelin stained less than the undamaged myelin, although here and there droplets of intensely staining material were found in the nerve and around the damaged area (mainly within microglial cells) in the brain.

Feyrter's Einschlussfärbung. The results of this method of staining were comparable to those obtained by the PAS and permanganate-Schiff technics. Metachromatic staining, at first diffuse, but mostly granular, appeared from the day after operation in the degenerating myelin. The metachromatic staining of degenerating myelin decreased more rapidly with time than the staining with PAS, and in the nerve most of the metachromasia was gone by the eighth to twelfth day after the operation.

Other procedures. The results of staining by the colloidal-iron technic were rather erratic; although in some instances good staining of degenerating myelin was obtained, no conclusions could be drawn from these experiments.

DISCUSSION

It is known, and the results of these experiments confirm the fact, that osmium tetroxide alone, directly or after dichromate treatment, will not differentiate degenerating myelin from normal tissue. The experiments corroborate the views of Swank and Davenport[7] that for the more efficient osmium tetroxide mixtures (Swank and Davenport's, and Busch's) pretreatment with dichromate is superfluous.

The fact that a differential dark staining of degenerating myelin can be obtained by the use of efficient oxidizing mixtures of osmium tetroxide with oxidants indicates that degenerating myelin probably contains a compound which can react with these mixtures, while normal myelin might either not contain it or else contain it in an unreactive or masked form.

Our knowledge on the range of reactivity of osmium tetroxide and osmium tetroxide-oxidant mixtures may be summarized as follows. Osmium tetroxide has long been known as capable of oxidizing ethylenic links, alcohols, phenols, naphthols, alpha-amino and alpha-oxy-acids.[8–12] The general belief at that time was that the osmium tetroxide is reduced to atomic osmium during the reaction, and this atom was considered to be the cause of the black color obtained. It has also been known since 1912[9] that osmium tetroxide can act in conjunction with other oxidizing agents, such as chlorates, whereby the osmium tetroxide serves as catalyst, oxidizing the substrate at first and getting reoxidized again from the reduced state by the chlorate. Further work[13–15] has shown that, with olefinic compounds, aromatic double bonds, and 1–2 diols, osmium tetroxide forms esters which are of brown-black color.

For the purpose of the present discussion these data indicate that an osmium tetroxide oxidant mixture is a stronger oxidant than osmium tetroxide alone. Furthermore, it is clear that the dark color produced may not be due to atomic osmium but rather to osmium-esters. Such esters can be formed by compounds containing ethylenic links as well as by many other molecular configurations, such as poly-alcohols.

The finding that staining of degenerating myelin in tissue sections yields inferior results as compared with the staining of tissue blocks points toward the possibility that the compound responsible for the staining of degenerating myelin might be soluble in water.

The results obtained with the PAS and permanganate technics indicate that degenerating myelin contains a greater quantity of available PAS reacting compounds from the day after cutting. While theoretically these compounds might be either carbohydrates or sphingolipids,[16] the last group of compounds probably may be disregarded in view of the data obtained by chemical estimations of lipids during demyelinization, which show no increase in any of the sphingolipids.[17]

The results obtained with Feyrter's method for metachromasia are less unequivocal. Without entering into the discussion as to the chemical basis of metachromasia, it might be assumed that the compound responsible for it is acidic in character.[18,19] It may be noted that Holmgren and Rexed[20] found metachromatic material in the Schwann cells of a peripheral nerve of the rat as early as one day after the nerve was sectioned. These authors used paraffin-embedded material and could not detect any metachromatic material within the axons and myelin.

It may be concluded that these experiments indicate that a carbohydrate compound (probably acidic) is rendered available for reacting during the early stages of demyelinization. Review of our knowledge on the reactions between osmium tetroxide-oxidant mixtures and organic molecules reveals that such a compound might be responsible for the Marchi type of staining. The fact that the different reactions appear at differ-

ent stages of demyelinization might be explained by a different sensitivity of the various reagents, or else by changes which occur in the structure of the hypothetic carbohydrate with time. These experiments appear to strengthen the case of the working hypothesis formulated as a result of a different approach to the same problem.[1] It seems probable that at an early stage of degeneration a carbohydrate compound is liberated from the myelin complex.

SUMMARY

Pieces of rats' sciatic nerves and brains were examined histologically at various intervals after transsection.

Differential staining of degenerating myelin has been obtained in sections treated directly by Busch's and Swank-Davenport's solutions. Degenerating myelin was found to react strongly with PAS and permanganate-Schiff stains, as well as with Feyrter's method for metachromasia from the day after transsection. These results, together with the known facts about the reactivity of osmium tetroxide-oxidant mixtures, are consistent with the notion that at an early stage of demyelinization a carbohydrate, possibly acidic, is liberated.

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Objective Comparison of Phenobarbital and Diphenylhydantoin in Epileptic Patients

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THE ANTIEPILEPTIC EFFECTS of phenobarbital have been known since 1912[1] and those of diphenylhydantoin since 1938.[2] Controlled comparisons of these two drugs, however, have not been reported. In 1950 Ruskin[3] stated, "Phenobarbital is still the most effective anticonvulsant in the treatment of grand mal epilepsy. Phenobarbital, if incompletely effective when used alone, is still more effective when supplemented with either Dilantin or Mesantoin than any single drug used alone or in other combination." The bases for these statements were the monthly seizure records of patients at the Caro State Hospital.

In any comparison of two or more medications, the results depend to a degree upon the doses which are chosen. It would be ideal to determine the maximum tolerated dose of each of the drugs in every subject and then to compare these. A more practical method is to administer the usual therapeutic dose. Diphenylhydantoin and phenobarbital are usually given in approximately the same quantities; therefore doses which were equal on a weight basis were chosen for this study.

METHOD

All patients were inmates of the Indiana Village for Epileptics. Most of them had evidence of focal brain damage. A few had normal intelligence; most of them were feeble minded. Adults of both sexes were used.

The patients were continuously under the supervision of ward personnel, who dispensed medications and reported convulsions. These attendants had been taught to differentiate minor focal seizures (without loss of consciousness) from major generalized convulsions (associated with loss of consciousness). For the purpose of analysis each minor attack was given a numerical value of one and each generalized convulsion a value of two. These arbitrary scores were assigned to give some estimate of severity without complicating the calculations of the results.

As indicated in the tables of results, two studies using different amounts of phenobarbital and diphenylhydantoin were completed. In each of these, the medications were given in equal numbers of identically appearing capsules three times daily (at 7:00 a.m., 3:00

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TABLE 1
RANDOMIZATION OF MEDICATIONS AMONG THE GROUPS OF PATIENTS

Series 1

A Phenobarbital gr. ½ and diphenylhydantoin gr. ½.
B Phenobarbital gr. ½
C Diphenylhydantoin gr. ½
D Blank

Group	Week *1st*	*2nd*	*3rd*	*4th*
1	A	B	C	D
2	B	D	A	C
3	C	A	D	B
4	D	C	B	A

Series 2

E Phenobarbital gr. ¾ and diphenylhydantoin gr. ¾
F Phenobarbital gr. ¾
G Diphenylhydantoin gr. ¾
H Blank

Group	Week *1st*	*2nd*	*3rd*	*4th*
1	E	F	G	H
2	F	H	E	G
3	G	E	H	F
4	H	G	F	E

p.m., and 11:00 p.m.). The patients and the attendants did not know which medication was given (double-blind test). For three days (Monday, Tuesday, and Wednesday) of successive weeks, the unknowns were substituted for the patient's regular medications. The seizure scores from these three days and the following day (Thursday) were used in the analyses.

In the initial study, the usual dose (gr. 1½) of phenobarbital and Dilantin was used. The second study was arranged at half standard doses in order to allow seizures with all medications and still obtain some measure of effectiveness. Four groups of six patients (selected because they repeatedly had seizures while unmedicated during a preliminary survey) were used in each study. The drugs were administered to these groups in the orders indicated in table 1 (Latin square design). In this method, at any time it appeared that some serious complication might occur as a result of the frequency or severity of the seizures, intravenous barbiturates were used to terminate the episode. It was not necessary to terminate the study prematurely in any of the 48 patients selected.

RESULTS

Detailed results consist of 2,304 seizure scores. Initial analyses showed that neither the groups of attendants (time of day) nor the weeks of the study produced significant effects. Therefore, the data were condensed into tables 2 and 5 without loss of significant details. Variance analyses of these data are presented in tables 4 and 7, respectively.

The column totals in both tables 3 and 6 indicate a progressive increase in the total seizure score when the unknowns were given. A decline occurs on the readministration of the patient's regular medications (fourth day). In both studies, this relationship among the four days is significant. This is an indication of the effectiveness of the regular medication the patients received, and measures by comparison the incomplete control of seizures by some of the medications during the test period. The row totals indicate that the greatest seizure score occurred with the blank. The blank was ineffective in controlling the seizures and this accounts to a large extent for the distribution of seizures among the days (see totals).

Statistically the difference in the effectiveness of phenobarbital and di-

TABLE 2

Patient's Number	A *Phenobarbital, 100 mg. Dilantin, 100 mg.* Days 1	2	3	4	B *Phenobarbital, 100 mg.* Days 1	2	3	4	C *Dilantin, 100 mg.* Days 1	2	3	4	D *Blank* Days 1	2	3	4
1											2					
2															2	
3							4		1	2	4	2			1	2
4		4	2							4	2	4				4
5											2	2	4	11	8	
6						6			4		2		2	2	4	2
7		1				3	6	10						8	4	
8														2	4	
9			4		2		1	2					2	4		2
10									4	2				1	4	8
11										4	2			1		
12			2					4				1			8	6
13											1			1		
14										1	2	6				
15															4	4
16						1									12	
17				2											2	
18								2	2	2	4		2	12	2	6
19															2	
20											2	1				
21															2	
22													2	3		
23						2			4		2	4		2	12	
24								1		2	2				6	8

The data obtained by scoring each focal activity as 1 and each generalized seizure as 2 points. Blank spaces indicate no convulsions during that period.

phenylhydantoin was not significant, nor was the direction of this difference the same in the two studies. Even when 100 mg. of phenobarbital or Dilantin were given, further improvement occurred when the other drug was added (A smaller than B or C in table 3). There was no indication that the combined effects were more than additive (E, F, and G not significantly different in table 6) when the smaller doses were used. In this second part, the total dose in milligrams was the same for the combination as for the drugs singly.

TABLE 3
THE SUMS FROM TABLE 2

Code	Medications	Days 1st	2nd	3rd	4th	Total
A	Phenobarbital, 100 mg.; Dilantin, 100 mg.	0	5	8	2	15
B	Phenobarbital, 100 mg.	2	12	11	19	44
C	Dilantin, 100 mg.	15	17	27	20	79
D	Blank	12	47	77	42	178
	Total	29	81	123	83	316

TABLE 4
ANALYSIS OF DATA REPORTED IN TABLE 2

Source of Variance	*Sum of Squares*	*Degrees of Freedom*	*Mean Square*
Patients	147.1	23	6.4‡
Treatments	157.5	3	52.5‡
Phenobarbital vs. Dilantin	(6.4)	(1)	6.4
Combined effect	(15.0)	(1)	15.0*
Blank effect	(136.1)	(1)	136.1‡
Days	46.4	3	15.5†
1 and 2 vs. 3 and 4	(24.0)	(1)	24.0†
1 and 3 vs. 2 and 4	(0.4)	(1)	0.4
1 and 4 vs. 2 and 3	(22.0)	(1)	22.0†
Remainder	1112.9	354	3.14
Total	1463.9	383	

*Significant at p = 0.05
†Significant at p = 0.01
‡Significant at p = 0.001

TABLE 5

	E *Phenobarbital, 25 mg. Dilantin, 25 mg.*				F *Phenobarbital, 50 mg.*				G *Dilantin, 50 mg.*				H *Blank*			
Patient's Number	*Days* 1	2	3	4	*Days* 1	2	3	4	*Days* 1	2	3	4	*Days* 1	2	3	4
25	2	4	2				6	4		2	2		2		2	
26											4					
27		10						1			1				20	
28																2
29				11			4									
30		2														
31											2				4	
32	1			2	1		6	21	3	6			2		12	
33		8	6	2		2	2		2	4	8		2	12		4
34							8	2								
35										4		2	2		2	
36		2	2					2			2	4				
37		2	2					2			3			2		6
38							2	2								
39			2							2	4			6	4	
40											2					
41													4			
42					2									2		
43			1			4			2	4			2		2	
44			2			2										
45		2	4			6		2		2		4		4	2	
46		8	4			3	4	2	2					6	8	
47	2						6					2	6	4	8	2
48										4	4					

The data obtained by scoring each focal activity as 1 and each generalized seizure as 2 points. Blank spaces indicate no convulsions during that period.

TABLE 6
THE SUMS FROM TABLE 5

Code	Medications	Days 1st	2nd	3rd	4th	Total
E	Phenobarbital, 25 mg.; Dilantin, 25 mg.	5	38	25	15	83
F	Phenobarbital, 50 mg.	3	17	38	38	96
G	Dilantin, 50 mg.	9	28	32	12	81
H	Blank	20	36	64	14	134
	Total	37	119	159	79	394

DISCUSSION

Most of the patients in this institution have received phenobarbital and/or diphenylhydantoin regularly for many years. It has been said that sudden withdrawal of antiepileptic drugs, especially phenobarbital, precipitates seizures and leads to status epilepticus. Medication was suddenly withdrawn from several hundred patients in order to select the groups used for this comparison. A few of these patients promptly developed seizures which were thought to be too frequent or too severe for them to receive a blank for three days. Others had only occasional seizures after one or more weeks and, therefore, could not be used. Still others had no seizures after several months withdrawal. With other drugs which produce physical dependence, the withdrawal syndrome has a fairly definite onset and offset. It is not probable, therefore, that withdrawal of anticonvulsant medication produces the seizures per se, but that the severity and activity of the epilepsy determines the seizure frequency. The experiment, as designed, therefore, tests the activity of anticonvulsive drugs in epilepsy and not in a withdrawal syndrome.

In epilepsy resulting from focal lesions, phenobarbital and diphenylhydantoin, in doses of equal weight, have approximately the same effectiveness. When given together the effects were additive. The maximum tolerated doses

TABLE 7
ANALYSIS OF DATA REPORTED IN TABLE 5

Source of Variance	Sum of Squares	Degrees of Freedom	Mean Square
Patients	336.2	23	14.6‡
Drugs	18.9	3	6.3
Phenobarbital vs. Dilantin	(1.2)	(1)	1.2
Combined effect	(0.2)	(1)	0.2
Blank effect	(17.5)	(1)	17.5*
Days	85.8	3	28.6†
1 and 2 vs. 3 and 4	(17.5)	(1)	17.5
1 and 3 vs. 2 and 4	(0.00)	(1)	0.00
1 and 4 vs. 2 and 3	(68.3)	(1)	68.3‡
Remainder	1871.8	354	5.29
Total	2312.7	383	

*Significant at $p = 0.05$
†Significant at $p = 0.01$
‡Significant at $p = 0.001$

were not determined; therefore, no comparison can be made of the maximum therapeutic effectiveness. The occasional occurrence of serious undesirable effects with diphenylhydantoin may be sufficient reason to consider phenobarbital the drug of first choice.

CONCLUSIONS

1. An efficient method for determining the effectiveness of antiepileptic drugs in blocking spontaneous seizures has been presented.

2. Phenobarbital and diphenylhydantoin, when given in equal amounts by weight, have approximately the same effectiveness in epilepsy resulting from focal lesions.

3. The combined effects of phenobarbital and diphenylhydantoin are additive.

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■ Suppose, for instance, a sword introduced from below upwards, or in the opposite direction, in the spinal cord, and dividing this organ into two lateral halves, and producing as little injury as possible to its anterior columns. The decussating fibres being then divided, sensibility would be lost in all the parts of the body from which these fibres come. It is hardly possible to conceive the production of such an injury, which is made with so much difficulty even in experimenting. But sometimes disease causes almost this kind of injury; for instance, a softening beginning in the very place where the decussation exists; or a slow increase of the amount of water in the central canal of the spinal cord may produce a greater diminution of sensibility than of voluntary movements. This is what occurs not rarely in the beginning of softening of the spinal cord, and in cases of spina bifida with hydrorachis. It would be very interesting to look for this symptom in cases of diplomyelia. Our learned friend Mr. Depaul has seen sensibility lost and voluntary movements partly preserved, in a case of division of the spinal cord (diplomyelia).

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

Psychomotor Seizures in Childhood

A Clinical Study

Gilbert H. Glaser, M.D. and Morris S. Dixon, M.D.

PSYCHOMOTOR SEIZURES are more common and important in childhood than realized previously and require differentiation from nonictal behavior disorders. In recent years, the increasingly great interest in these seizures has tended to focus on the problem in the adult. Fostering this were considerations that psychomotor seizures were rare in children[1] or in such a low incidence as 5 per cent.[2] However, in certain series it had been estimated that 20 to 25 per cent of cases have an onset before the age of 15.[3–5] In a more recent survey, Bicard, Gastaut, and Roger[6] found an even higher onset in childhood: an incidence of 45 per cent before the age of 15, with 8 per cent prior to age three. In addition, 45 per cent of all seizure cases in their group below the age of 15 had psychomotor seizures. The increased recognition of these states is implicit in their determination that, in the adult group over the age of 26, up to 95 per cent of all patients had psychomotor seizures. Furthermore, studies of the pathogenesis of this type of seizure have suggested that many cases may have their origin in lesions occurring at birth, such as incisural sclerosis produced by hippocampal herniation[7] or as a result of head injuries or encephalitis in childhood.[5,8]

Psychomotor seizures are characterized usually by auras of anxiety and visceral symptoms, followed by alterations in consciousness associated with many varied complex feeling and thinking states, and automatic somatic and autonomic motor behavior. These phenomena are associated with at least a partial amnesia. In many instances a chronologic sequence of motor events may occur, evolving in brief phases.[9] First there may be an arrest or suspension of activity with perhaps a simple nonrepetitive movement. This is followed by repetitive, stereotyped automatisms with little variation from seizure to seizure, such as swallowing, sucking, or chewing and movements of the arms and legs. The third phase, which dominates the picture in the adult, consists of automatic acts of varying complexity, semipurposeful, inappropriate, and bizarre, involving an interplay with the environment and determined in part by psychologic factors. The activities in this latter phase often may appear to merge into normal behavior.

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In children, however, the phenomena of the first two phases or only a simple isolated automatism have been reported to be predominant.[4,10]

The electroencephalographic abnormalities in adults consist of diffuse theta activity and a high incidence of focal unilateral or bilateral temporal (especially anterior) spikes or sharp waves. Gibbs and Gibbs[5] have found an 88 per cent incidence of unilateral anterior temporal foci, brought out in 50 per cent of their cases by sleep. Others[8,11,12] have shown a lower incidence of such foci and higher occurrence of bilateral temporal abnormalities. The electroencephalograms associated with psychomotor seizures in childhood show a much greater variety of abnormality.[13] Focal temporal spikes are relatively infrequent (10 per cent) and are elicited in only slightly higher incidence by sleep. There is, in addition, a striking association of slow spike-wave discharges with psychomotor automatisms in children. The problems of classification and relation between psychomotor seizures and temporal lobe epilepsy have been reviewed thoroughly by Gastaut.[8] He also emphasizes the nonspecificity of the electroencephalogram in early childhood.

The present study was undertaken in order to clarify further the clinical picture of psychomotor seizures in children and to delineate more clearly the problems of diagnosis and treatment of this disorder in the young. It is based on an intensive clinical analysis of psychomotor seizure states in 25 children.

CASE MATERIAL AND METHOD OF STUDY

The selected case material in this series consisted of 25 children between the ages of one and one-half and 16 studied in the neurology and pediatric outpatient services of the Yale-New Haven Medical Center. There were 15 boys and ten girls. These cases were selected from a total patient roster of approximately 200. The incidence of children with psychomotor seizures in the entire group was about 30 per cent of the total cases. The selection was based mainly on availability for studies, follow-up, and our ability to obtain complete information concerning the seizures and interseizure behavior from the patient and the family. The seizure patterns were regarded by at least two observers in each instance to fit the criteria as defined above for psychomotor epilepsy. None of these children had a history of petit mal seizures. Only three had a history of one or a few grand mal convulsions occurring in the past and usually associated with fever in infancy or early childhood. In no patient was the presence of concomitant grand mal seizures a factor during this present study.

All the patients received complete medical and neurologic evaluations, including electroencephalograms and roentgenograms of the skull. The electroencephalograms were performed with standard 16 to 20 electrode bipolar and monopolar recording technics using eight-channel Grass equipment. Recordings were obtained during the waking state at least once from all patients and during sleep in 18 instances. The sleep was natural in eight and Seconal-induced in ten.

In many instances seizures were observed by physicians, and occasionally an electroencephalogram was recorded during a seizure. The seizure descriptions were obtained usually from the relatives of the patient, aside from the instances of observation by a physician or other hospital personnel. The attempt was made by the physicians involved in this study to establish a close relationship with the children, and during many clinic visits the child was encouraged to describe any recalled feelings and events associated with his episodes. In addition, an evaluation was made of the child's interseizure behavior both at home and at school. For this, information was obtained from relatives, social workers, and school teachers. Lumbar punctures and pneumoencephalograms were performed when indicated in several instances. A complete battery of psychometric tests could be per-

formed satisfactorily in only 12 cases. All patients were followed at appropriate intervals during a period of two years.

GENERAL FINDINGS

The age at onset of the psychomotor seizures in this group was determined and is presented in table 1. Three of the children had the onset of seizures between the ages of less than one year and three years. The onset in nine children was between the ages of four and six, in eight children between seven and ten years, and in five children between 11 and 16 years. The duration of the seizure disorder varied from two months to eight years at the time of the initial evaluation in this project. A positive family history for grand mal seizures was present in three instances. No family history of psychomotor seizures was obtained.

Possible etiologic factors of significance in the past history were present in 15 cases, or 60 per cent of the series. Six children had a difficult delivery with prolonged labor. One child had a premature birth, otherwise uncomplicated. Central nervous system infections such as encephalitis or meningitis had occurred in four patients, and severe trauma and postnatal anoxia were factors in one case each.

The general physical examination was normal in all instances. Two of the children had smaller skull circumferences than average for their age. Otherwise the neurologic examination was essentially negative in all of the children. All of the skull films were normal, with the exception of a skull asymmetry in the child of premature birth. This child also had an abnormal pneumoencephalogram, with enlargement of the right temporal horn suggestive of porencephaly. Pneumoencephalography was performed in four other instances, with normal findings in three and slight right frontal atrophy in one. The cerebrospinal fluid of nine children was within normal limits with regard to pressures, cells, protein, and serology. The blood serology was normal in all instances.

TABLE 1

PSYCHOMOTOR SEIZURES IN CHILDHOOD

Age at Onset (years)	*Number of Patients*
1 to 3	3
4 to 6	9
7 to 10	8
11 to 16	5

SEIZURE MANIFESTATIONS

An analysis of the various manifestations associated with the psychomotor seizures of these children is presented in table 2. The children were divided into two age groups, from one to six years and from seven to 16 years. Sixteen children experienced auras of intense anxiety, usually but not always associated with visceral sensations. These feelings were remembered quite clearly in all instances of children over six years of age (ten cases); however, the six younger children had a very definite recollection of an ill-defined unpleasant sensation prior to the spell. Symptoms referable to nausea or a peculiar epigastric sensation were present in 11 instances. In 14 cases, however, an epigastric sensation associated with nausea or vomiting appeared to be an actual early part of the seizure, and four patients experienced severe abdominal pain which often caused clutching movements at the upper abdomen.

Some alteration of consciousness occurred in all cases, but a total loss of consciousness did not occur. The change in awareness was followed usually by an alteration in trunk or limb position, staring, and oral movements such as lip smacking with drooling, spitting, muttering, mumbling, and hissing sounds. Integrated but confused automatic movements occurred next, often with aimless wandering, fumbling hand activity, and incoherent, irrelevant speech. Many of the children showed some affective disturbance such as fear or anger during the seizure, and this often was associated with severe aggressive behavior. Three of the older children experienced peculiar perceptual dis-

TABLE 2

SEIZURE MANIFESTATIONS

Seizure Manifestations	Number of Patients (Total 25)		
	Age 1 to 6	Age 7 to 16	Total
1. Aura	6	10	16
2. Altered consciousness	12	13	25
3. Change in position of body or limbs	10	11	21
4. Integrated but confused activity	8	11	19
5. Staring or dazed expression	10	8	18
6. Epigastric sensation, nausea, vomiting	9	5	14
7. Oral movements, drooling	8	5	13
8. Muttering, mumbling, hissing	5	5	10
9. Walking, wandering	4	6	10
10. Pallor or flushing	5	4	9
11. Rubbing or fumbling	4	5	9
12. Speech (usually irrelevant or incoherent)	3	5	8
13. Affective disturbance (fear, anger)	5	3	8
14. Stiffening of body or limbs	5	3	8
15. Falling	4	3	7
16. Aggressive activity	4	3	7
17. Dreamy state	2	3	5
18. Forced thinking or ideational blocking	1	4	5
19. Searching or orienting movements	1	3	4
20. Abdominal pain	3	1	4
21. Incontinence (urinary)	2	1	3
22. Perceptual disturbance (visual, auditory)	0	3	3

turbances during the seizure, indicating that objects or sounds appeared either closer or farther away. An amnesia was present for most of the events of the seizure in all instances, especially the automatisms. The duration of the seizures varied from about one minute to over one hour.

There were only slight differences between the two age groups with regard to the basic seizure patterns. The younger children tended to give less detailed accounts of the initial aura or early phase of the seizure. Also, the interaction of this group with the environment during the automatism was less complex. Evidence of visceral involvement such as retching and clutching at the epigastrium or abdomen was extremely frequent in the younger group. The more complicated patterns involving thoughts, verbalizations, and perceptual disturbances occurred more frequently in the older children.

INTERSEIZURE MANIFESTATIONS

The varied interseizure manifestations are presented in table 3. Nineteen children had significant personality disturbances appearing between their psychomotor seizures. There was some correlation between the frequency of seizures and the behavioral disturbance. The children with more frequent seizures tended to have more disturbed behavior, although in two instances behavior worsened as seizures lessened. Also, it seemed that the interseizure behavioral disturbance increased in intensity and variability as time went on after the onset of the disorder, especially if the seizures did not come under control. Intense nervousness, irritability, and excitability were common, as were stubborness, compulsiveness, hyperactivity, and impulsive aggressive behavior. These children tended to react poorly in school environments and at home, and developed very difficult relationships with

TABLE 3
INTERSEIZURE MANIFESTATIONS

Interseizure Manifestations	Number of Patients (Total 25) Age 1 to 6	Age 7 to 16	Total
1. Excitability, irritability, "nervousness"	10	9	19
2. Stubborness, compulsiveness	6	8	14
3. Hyperactivity	8	6	14
4. Aggressiveness	7	7	14
5. Temper tantrums	6	3	9
6. Depression	2	7	9
7. Somnolence or insomnia	2	5	7
8. Nightmares	4	2	6
9. Headaches	1	5	6
10. Intellectual deficit	2	4	6
11. Phobias	1	3	4

their siblings or fellows at school. Sleep disturbances with nightmares, night terrors, insomnia, or somnolence were frequent, and the children often recalled terrifying dreams. No actual overt psychotic or clearly autistic behavior appeared in this group. However, many of these children were regarded as severe behavior problems in their adjustments at school or at home.

There were some differences between the two age groups. The younger children had a greater tendency toward severe temper tantrums and nightmares. The older children were able to describe more complex psychologic disturbances such as depressive symptoms and phobias, and in addition, were more subject to headaches and insomnia. The impulsive, aggressive, hyperactive behavior was a common denominator in both groups and many of the children had more than one type of disturbance.

The psychometric tests performed in 12 children revealed intellectual deficit in six, with intelligence quotients ranging between 70 and 80. In many instances the projective tests such as the Rorschach showed evidence of difficulty with control of violent, hostile, aggressive impulses.

A few children showed oscillations in behavior between good, quiet, cooperative activity and impulsive, violent, destructive activity. These changes were not clearly associated with seizures and could be differentiated from them.

Some interseizure difficulty in language and speech appeared in five cases, not correlated with any electroencephalographic focus, but in children who had abnormal verbalizations as part of the seizure. These children were uniformly slow to learn to read and spell but were not definitely aphasic, apraxic, or agnostic.

ELECTROENCEPHALOGRAPHIC FINDINGS

The electroencephalograms of these 25 children revealed normal or borderline records (three cases); focal spikes temporally (five cases), bitemporally (four cases), and frontally (two cases); focal slow waves temporally (two cases), and frontally (two cases); bilateral diffuse slow (1½ to 2 cycles per second) spike-wave discharges (five cases), and bilateral synchronous delta activity (two cases). These findings include the combined results of all recordings performed both during the waking state and sleep. The sleep recording showed additional focal temporal spiking and bitemporal spike activity in only one instance each when not present in the waking state. In three cases temporal spike or sharp wave activity present in unclear fashion during the waking state was more clearly delineated during sleep. Otherwise, the recording during sleep was noncontributory and in three instances slow wave foci present in

TABLE 4

ELECTROENCEPHALOGRAPHIC FINDINGS

EEG Classification	Number of Patients		
	Age 1 to 6	Age 7 to 16	Total
Normal or borderline	1	2	3
Focal temporal spikes	2	3	5
Bilateral temporal spikes	2	2	4
Focal frontal spikes	1	1	2
Focal temporal slow waves	1	1	2
Focal frontal slow waves	1	1	2
Bilateral diffuse slow spike and wave (1½ to 2 cycles per second)	3	2	5
Bilateral synchronous delta	1	1	2
Totals	12	13	25

the waking state were obscured. There were no major clinical differences associated with the various groups of electroencephalographic abnormalities. The patients with predominantly temporal abnormalities exhibited similar auras and automatisms to the other groups, even to those with spike-wave discharges. However, the three children with perceptual disturbances during the seizure showed either bilateral temporal spike activity or focal temporal slow waves. As seen in table 4 there were no significant differences in the incidence of the electroencephalographic findings between the two age groups of the children.

RESULTS OF TREATMENT

These children have been treated with a variety of anticonvulsant agents singly or in combination. In particular, diphenylhydantoin (Dilantin), phenobarbital, mephobarbital (Mebaral), methylphenylethylhydantoin (Mesantoin), trimethadione (Tridione), paramethadione (Paradione), primidone (Mysoline), the amphetamines, and acetazolamide (Diamox) were used. Phen-

TABLE 5

RESULTS OF DRUG TREATMENT

Degree of Control	Number of Patients	
1. EXCELLENT (75 to 100 per ecnt)	7	
Diphenylhydantoin and phenobarbital		5
Diphenylhydantoin		1
Primidone		1
2. GOOD (50 to 75 per cent)	8	
Diphenylhydantoin and phenobarbital		5
Diphenylhydantoin and mephobarbital		1
Diphenylhydantoin and primidone		2
3. FAIR* (25 to 50 per cent)	7	
Diphenylhydantoin and phenobarbital		4
Diphenylhydantoin and primidone		3
4. POOR* (0 to 25 per cent)	3	
Diphenylhydantoin and phenobarbital		2
Diphenylhydantoin and trimethadione		1

*Other drugs tried in these groups: mephobarbital, methylphenylethylhydantoin, trimethadione, paramethadione, amphetamine, and acetazolamide.

acemide (Phenurone) was regarded as too toxic and was not administered to our patients. Many patients had received one or more of these medications prior to our evaluation. All of the cases have been followed up to two years. An over-all presentation of the results of treatment and the final drug used in these patients is shown in table 5. The degree of control is presented as percentage of seizure elimination. Excellent control (75 to 100 per cent) was achieved in seven patients, good control (50 to 75 per cent) in eight patients, fair control (25 to 50 per cent) in seven patients, and poor control (0 to 25 per cent) in three patients. Therefore 22 of our patients come under some control, with 15, or 60 per cent, achieving good to excellent results. There was no correlation between the response to anticonvulsant medication, specific seizure pattern, or type of electroencephalographic abnormality. The electroencephalogram was repeated during treatment in 16 cases. Improvement in abnormality occurred in ten instances, especially those with spike-wave discharges. The temporal spikes and focal or diffuse slow waves were less responsive. Complete normality was achieved in only four records and paralleled clinical improvement. The seven patients with excellent control achieved this with diphenylhydantoin and phenobarbital, diphenylhydantoin and mephobarbital, or diphenylhydantoin and primidone. Therefore it would appear that in this group diphenylhydantoin, especially in combination with phenobarbital or primidone, is the most effective anticonvulsant. Although methylphenylethylhydantoin (Mesantoin) was effective in three cases, it produced leukopenia in all, and it was necessary to substitute diphenylhydantoin in each instance. Neither trimethadione nor paramethadione was significantly effective even in patients with spike-wave discharges in the electroencephalogram, and either one or both of these drugs was administered to all of these patients. The amphetamines, such as Benzedrine, had no influence on the overactive, aggressive behavior or on the seizures in any instance. Acetazolamide (Diamox) was administered to three patients and did not alter the seizure frequency. Surgical intervention was not considered in any patient.

We were able to place only five of the patients with severe interseizure behavioral difficulties under psychiatric guidance. This therapy and the working out of intrafamilial problems had a very salutary effect on both the behavior and the seizure frequency in this small group.

DISCUSSION

This analysis of psychomotor seizures was especially designed to evaluate the clinical manifestations as they appear in children. There have been only a few previous studies specifically oriented toward this problem. Lennox[4] has emphasized that psychomotor seizures in children were mainly of the "psychomotor" proper type in his classification, with either an increase or arrest of movement or simple primitive automatisms. He found a relatively high incidence (33 per cent) of antecedent brain damage in his cases; in our present series this was 60 per cent. Nekhorocheff and Lerique-Koechlin[10] also described simple monosymptomatic automatisms and visceral crises in infants and children, and emphasized the frequent occurrence of psychologic disorders with night terrors and behavioral difficulties. Robertiello[14] reported the cases of three children with psychomotor seizures and emphasized that the differential diagnosis should be made between these seizure states, the other nonictal behavioral disorders, and childhood schizophrenia. He also pointed out the problem of the difficulty that these children have in controlling their violent aggressive emotions, which leads to expression in impulsive behavior disorders. In our present series the most common manifestations in any age group were auras with anxiety symptoms, visceral phenomena, various oral movements, and both simple and moderately complex bodily actions or automatisms. Also, in our patients the interseizure period

contained a high incidence of abnormal tense, overactive aggressive behavior.

The paroxysmal or usually sharply episodic nature of the psychomotor seizure and the concomitant alteration of consciousness or awareness serve to differentiate it from nonparoxysmal behavior disorders. However, the interseizure psychologic disturbance is more difficult to categorize. It appears to be essentially a conduct disorder, most likely secondary to both the organic cerebral dysfunction which produces the seizure state and personality factors conditioned environmentally. One can only conjecture concerning the influence of intermittent subclinical seizure discharges as seen in the electroencephalogram, such as focal or bilateral temporal spike and bilateral spike-wave discharges, on the functions of the cerebral cortex and subcortex, and the way in which this affects nonseizure behavior and interaction with the environment. The interseizure behavioral disorder in these children resembles closely that seen in post-encephalitic states, as characterized by Bender.[15] The children in both of these groups have difficulty in relation to the outside world, especially in social relationships. This is shown by the restlessness, hyperactivity, egocentricity, and motivation by self interest, and asocial and antisocial trends develop along with emotional instability, lability, and lack of inhibition. In addition, the behavioral disorders described by Bradley[16] are exaggerated in our group. He found a cluster of traits commonly associated with epileptic children: erratic variability in mood and overt behavior, hypermotility or driveness, irritability with low threshold often bringing the child into difficulty with the environment, short attention span, and distractibility and difficulty with certain learning processes in school such as mathematics, reading, and spelling. Several of our children had language and speech disturbances appearing either as abnormal verbalizations during the seizure or very slow learning of reading and spelling. Some of these children had problems related to laterality. However, none was truly aphasic, agnostic, or apractic. In addition, there was no correlation with electroencephalographic abnormality. Similar cognitive deficits in older patients with psychomotor seizures have been described recently by Quadfasel and Pruyser,[17] who regard the basic impairment as one in verbal memory. They also were not able to correlate this defect with any focal discharges in the electroencephalogram. There is an additional parallel in the high incidence of interseizure psychiatric disturbances in adults with psychomotor automatisms. These vary from mild to severe psychoneuroses and character disorders to overt psychotic reactions.[18–20]

The analysis of electroencephalographic patterns may be of some help in distinguishing between children with psychomotor seizures and those with functional nonepileptic behavior disorders. There have been many reports of the association of diffuse slow wave abnormalities in children with functional behavior disorders.[21,22] Occasionally in these children and older persons, even paroxysmal patterns may occur.[23,24] However, the latter are usually runs or bursts of 4 to 6 cycle per second theta activity without spike potentials. The paroxysmal electroencephalographic abnormalities present in children with psychomotor seizures are basically either bilateral spike-wave discharges or unilateral or bilateral spikes or sharp waves from the temporal regions. In a previous report[13] we have reviewed the various electroencephalographic patterns associated with psychomotor seizures in childhood. In general, the findings in the present smaller series resemble those of the larger group which was studied mainly from the electroencephalographic standpoint. In particular, the relatively high incidence of generalized spike-wave discharges of 1½ to 2 cycles per second frequency, rather than the focal temporal spikes has been commented upon as a major difference between the psychomotor seizure states in children as compared with those of adults. These spike-

wave discharges occurred with seizures of short or long duration. Also, a relatively minimal additional localization is obtained during sleep. These findings were related to the immature cerebral cortex of the child involved in abnormal electrical discharges between the interconnected temporal-limbic and thalamoreticular or centrencephalic structures.[25] It was postulated that either of these nuclear or gray matter aggregations may be the site of origin of psychomotor seizures in children. This would mean that, aside from an origin predominantly from the temporal or limbic structures, in some instances psychomotor seizures may originate from subcortical, central nuclei, or possibly other cortical areas discharging centripetally into these. In addition to the cases with spike-wave discharges in our report and those from the literature discussed previously,[13] several more have been reported recently.[26–29] We have preferred to regard these automatisms associated with spike-wave discharges in the electroencephalogram as true psychomotor seizures rather than prolonged petit mal or petit mal automatism,[25] since we feel that this latter designation confuses the definition of petit mal seizures and extends it into a different more complex phenomenon. There have been no significant clinical differences in our cases between seizures with spike-wave discharges and those with unilateral or bilateral temporal discharges.

The patients in our series were treated mainly pharmacologically in the setting of a clinic relationship. In a few instances intensive psychotherapy was an effective adjunct. Neither the seizure frequency nor the behavioral disturbance was severe enough in any case, even with a focal electroencephalogram, to warrant surgical intervention. The most efficient drug combination was that of diphenylhydantoin and phenobarbital, but even here an over-all good control was obtained in only about 60 per cent of the patients. This result is similar to those cited in previous reviews, mainly concerning adult patients.[30–32] In a few instances primidone was effective, usually together with diphenylhydantoin. The experience of other groups with primidone has been variable, the reports ranging from no effect[33] to occasional good control.[34,35] The diones were not effective even in patients with spike-wave discharges. However, the spike-wave discharges in our group were not of the typically synchronous 3 cycle per second spike-wave variety as seen also in petit mal epilepsy. When the latter electroencephalographic abnormality is present, trimethadione may be an effective anticonvulsant.[28,29] There was no correlation in our series, however, between the type of seizure, the electroencephalographic disturbance, and the response to therapy.

SUMMARY

Psychomotor seizures are more common in childhood than realized previously and require differentiation from nonictal behavior disorders. An intensive clinical analysis was made of seizure manifestations and problems in diagnosis and treatment. Twenty-five children had seizures characterized by auras of anxiety and visceral symptoms, followed by changes in consciousness associated with many varied, complex feeling and thinking states, and automatic somatic and autonomic motor behavior. At least a partial amnesia occurred in all instances. Nineteen children had interseizure personality disturbances mainly characterized by overactive, aggressive behavior. Etiologic factors in the background such as birth trauma and central nervous system infection were in high incidence (60 per cent). The major abnormalities in the electroencephalogram were either unilateral or bilateral temporal spike or bilateral, diffuse, slow spike-wave discharges. In particular, the electroencephalographic findings are felt to implicate both the temporal-limbic and centrencephalic systems. There were no major clinical differences between these groups, nor were there any major differences between younger and older children except for the predominance of more sim-

ple automatism in the younger group and the higher occurrence of more complex thought disorders in the older. Twenty-two children achieved some measure of control with diphenylhydantoin in combination with phenobarbital or primidone. The diones were ineffective. However, relatively satisfactory control of seizures was obtained in only 60 per cent of the cases, and it is felt that there is still a great need for a more effective anticonvulsant medication for psychomotor seizures. Also, the psychologic problems involved in this group require much further evaluation and understanding.

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CLINICAL PATHOLOGIC CONFERENCE

E. P. Richardson, Jr., M.D. Section Editor

Presented by *Rhett Talbert, M.D., D. Denny-Brown, M.D. and Margaret C. Swanton, M.D.*

CASE PRESENTATION

DR. RHETT TALBERT: The case that we have this morning is that of a five year old girl who was admitted to the Roper Hospital in Charleston on July 26, 1955 with the complaint given by her mother that "she falls all the time and has been vomiting." The child had been in perfectly good health except for occasional head colds until three weeks before admission, when the mother noticed that she staggered as she walked and fell frequently. About a week later the right eye was inflamed and her eyes "seemed weak." The right eyelid was observed to remain partially open during sleep, and shortly thereafter her mother noticed that when she smiled her mouth pulled to the left. She continued to play around the house, seemed afebrile, and had no other symptoms. However, her staggering became progressively worse. Two days prior to admission she was standing on a couch and fell from it, apparently not hurting herself. There was no evidence that she hit her head during the fall. On that same day she began vomiting and became progressively lethargic during the 48 hours prior to admission. There was no history of convulsions or other pertinent illness, and the child had not had diarrhea. Except for a minor head cold about two weeks before the onset of the illness, she had had no other symptoms.

The child was the product of a full-term pregnancy and normal delivery, with a birth weight of 8 pounds, 4 ounces. She was breast fed. Her early development was normal in every way. She had received DPT inoculations at the usual age and had had appropriate "booster shots" annually since then. She had also been immunized against typhoid fever at an earlier age and she had received a smallpox vaccination on June 1, 1955, approximately five weeks before the onset of the present symptoms.

The family history was noncontributory. There were four sisters and three brothers, all of whom were living and well.

On examination at the time of admission the child was found to be well developed and nourished, slightly dehydrated, and the general appearance was that of a sleeping child. She could be aroused from her sleep and responded briefly by saying "Huh" or other very simple response. She would open her eyes momentarily and would even cooperate briefly for testing, but then she lapsed back into sleep again during the examination. She was having occasional episodes of vomiting which were nonprojectile. Her temperature on admission was 101° F., the pulse rate was slightly elevated, and respirations were regular, 22 per minute, and slightly shallow. Her color, however, was good. Her head was normal in size and shape. The neck was not stiff. Funduscopic examination showed the disks clearly outlined, veins not distended, and there was a physiologic cup bilaterally. There was a right internal strabismus. She followed the moving finger poorly with her eyes and could not be induced to look to the right with either eye. She did look to the left and in other directions to some extent, and on attempting to look up there was

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a sustained vertical nystagmus. The corneal reflex was absent on the right. The child was extremely lethargic at this time, but there was a distinct and consistent difference between her arousal when she was pricked on the left side of her face and failure to arouse when she was pricked on the right side of her face. The right palpebral fissure was wider than the left and the eye would not close completely as she lay sleeping. A right facial weakness was evident on grimacing. She made no response to sound introduced near the right ear, whereas occasionally a sound stimulus near her left ear caused her to turn her head to the left side. She would not protrude her tongue. There was a weak gag response bilaterally. Mucus was accumulating in her throat, requiring frequent aspiration. She lay very quietly in bed for the most part and there was little spontaneous motor activity. When she did change positions occasionally she seemed to move all of her limbs equally. On passive movement of the limbs there was a generalized hypotonicity. The tendon reflexes were hypoactive but symmetric throughout. The plantar response was extensor on the right and equivocal on the left. She withdrew all limbs from painful stimulation. Except for occasional scattered rhonchi on auscultation of the lungs, the physical examination was within normal limits.

On the following day the neurologic findings were unchanged, except that on attempting to follow the examiner's finger she would open her eyes and look at the finger but was not able to follow in any direction except downward. Also there was no movement in any direction except downward on passively turning the head. At rest there was a slight internal deviation of the right eye. The pupils were each 4 mm. in diameter and they reacted briskly to light. When called she answered in very simple grunts or sounds, but she would not otherwise vocalize and could not be induced to speak beyond monosyllables. At this time the left plantar response was extensor and the right equivocal. She withdrew all limbs from pin-prick.

Laboratory studies. Hemoglobin 13 gm.; red cell count 4,100,000; white count 16,200, with 86 per cent polymorphonuclear cells and 14 per cent leukocytes. Urine was normal. Lumbar puncture: opening pressure 140 mm. of spinal fluid, fluid clear and colorless, containing one lymphocyte, 60 mg. per cent sugar, 40 mg. per cent total protein, colloidal gold 0121100000, culture negative. Blood serology was negative. Skull films were normal except for slight accentuation of digital markings. The mastoid cells and petrous pyramids were normal. Electroencephalogram revealed rhythmic bilaterally synchronous slow-wave activity without evidence of a focal cerebral lesion; the patient was sleeping during the tracing.

She was treated with intravenous fluids and a stomach tube was put down. She had to continue having frequent aspirations of her oropharynx for accumulating mucus. She was given a variety of antibiotics. The temperature remained slightly elevated for the first week of hospitalization and then became normal. The pulse rate also became normal about the same time as the temperature. She remained in this lethargic, semicomatose condition until the fourth hospital day when she became gradually more alert. She began to move around more, opened her eyes and looked around, and answered questions a little more completely than she had previously. It then became apparent that in the movement of the left upper extremity, as in reaching for things, there was a very marked ataxia; also when she was asked to raise her lower limbs separately there was an ataxia of the left one. When she was placed in the sitting position, she wobbled back and forth, unable to maintain the sitting posture without supporting herself. When she reached to support herself with her left hand, it became evident that there was a marked wide amplitude tremor of the left upper extremity. Throughout the remainder of her hospital course she became progressively more alert. She began chatting with the other patients on the ward and she began to take fluids and soft foods by mouth. Toward the end of the second week of hospitalization she was able to maintain nutrition entirely by oral feeding. The eye movements improved to the degree that she would follow to some extent in all directions without nystagmus, but she still seemed to prefer a left conjugate position of the eyes. The analgesia of the right face could no longer be demonstrated, but the right corneal reflex remained diminished. She became able to stand up with support, but she was extremely unsteady on her feet and could not take steps alone. With help she could take crude steps in a very ataxic and unsteady fashion. She remained weak in all extremities and the ataxia of the upper and lower extremities on the left remained present. She was discharged home on August 24, about four weeks after admission.

She was readmitted to the hospital on September 12. At that time her mother stated that she had continued to improve slowly at home following discharge, but on September 1 she began to complain for the first time of a right-sided headache. A week after that she again began vomiting. Her speech was slurred and she became somnolent again.

On examination at the second admission she appeared very pale, lethargic, and barely responded when shaken and called. The pupils were equal. There was slight papilledema, more marked on the right. The tongue fell backward in the mouth and mucus was again accumulating in the throat. She was barely able to move the limbs. Her plantar responses were bilaterally extensor. A repeat lumbar puncture done at this time showed a pressure of 130 mm., one lymphocyte, total protein of 21 mg. per cent, and sugar 70 mg. per cent. The following morning as the child was being turned on her side, she suddenly died.

QUESTION: Was there no evidence of ear disease and no stiff neck?

ANSWER: No. The ears were normal on examination and there was no history of ear infection. Throughout her hospitalization there was no nuchal rigidity, even when she became more alert.

QUESTION: On the second admission did she still have the cranial nerve palsies?

ANSWER: She was admitted in the evening in a state of marked depression of consciousness and died the next morning. There is no detailed examination of the cranial nerves recorded. The information given by the mother did not indicate any further improvement in these between the two hospitalizations.

QUESTION: Was it known whether she had any sort of systemic reaction following smallpox vaccination?

ANSWER: No, there was no reaction as far as we could ascertain from the history.

DISCUSSION

DR. D. DENNY-BROWN: Even though the opening lumbar puncture pressure was not raised at the time of either first or second admission, the history of frequent vomiting, progressive lethargy, together with progressive unilateral cranial nerve paralysis, should point to the presence of distortion of structures in the posterior fossa. The vomiting of increased intracranial pressure is frequently nonprojectile. Very early in the story there was evidence that there was right facial paralysis, peripheral in type because closure of the eye was affected. Indeed the child must have had some traumatic inflammation of the cornea. So we suspect that a very early feature of the pathology involved the seventh nerve on the right side, developing at the same time as a staggering gait and frequent falling, indicating cerebellar or vestibular disturbance. At the time of admission there was also noted some involvement of the fifth, sixth, and eighth nerves on the right side. The statement that the patient had vertical nystagmus and could not deviate the eyes to the right could indicate either damage to the corticobulbar fibers in the left side of the brainstem or gross displacement of structures in the right side of the brainstem. The greater involvement of the right sixth nerve in the beginning, the loss of all conjugate movement except downward during the first admission, and the involvement of other nerves on the right side all lead me to the conclusion that this was a right-sided disturbance of the mechanism of lateral gaze, perhaps the vestibular mechanism, rather than corticobulbar innervation. Evidently this process did not extend below the level of the pons because the tongue and palate moved symmetrically, or as high as the midbrain because the pupils remained symmetric and reactive. Neck rigidity and respiratory embarrassment might have been expected if there was herniation through the foramen magnum, but their absence does not deny such herniation. The left extensor plantar response was further indication of lesion of the right side of the pons, but the absence of long sensory tract disturbance and the later predominance of left-sided cerebellar signs show that the anatomic lesion was not clear-cut or limited to the right side of the pons.

Up to this point the history indicates the development of a posterior fossa disturbance with cerebellar signs, embarrassment of the medullary functions by pressure or displacement, and damage to the right fifth, sixth, seventh, and eighth cranial nerves. The absence of papilledema leads me to believe that hydrocephalus was not of critical degree, and the early recovery from

lethargy and other signs indicate severe distortion of the brainstem rather than destruction of it. I would be thinking in terms of some pathology in the lateral posterior fossa on the right side, developing rather slowly and insidiously in a period of three weeks. There is no evidence of aural disease, so any process beginning in the middle ear and involving cranial nerves by inward extension or by venous metastasis is unlikely. The spinal fluid findings do not indicate any inflammatory reaction. Smallpox vaccination on June 1 is noted, but postvaccinial encephalomyelitis would have evolved more rapidly about 14 days after the vaccination, with more symmetric lesions and inflammatory reaction. Though the fever suggests inflammatory disorder, the spinal fluid report of one lymphocyte, 47 mg. per cent total protein, and 60 mg. per cent sugar denies the presence of any inflammatory meningeal reaction. The accentuation of digital markings in the skull suggests a possibility of longer standing increase in the intracranial pressure than does the clinical history, but is not in itself adequate to lead us definitely to that conclusion. The slow rhythmic electroencephalographic abnormality would be consistent with a mild degree of internal hydrocephalus and also not contributory in relation to the pathology of the process.

The spinal fluid findings and our preliminary conclusions from the history now lead us to consider brain tumor as a probable pathology. The lateral recess is a very unusual place for primary tumors in children of this age, and acoustic neuroma is a very slow process indeed. This illness evolving in less than two months points to a different cause. The common rapidly evolving tumor in the posterior fossa in childhood is medulloblastoma. The early symptoms of seventh nerve paralysis would imply that the tumor had commenced in the lateral part of the brainstem on the right side, an unusual and unlikely place for medulloblastoma. Ependymoma begins more in relation to the ventricular system, making early seventh nerve paralysis unlikely.

Only the glioma pontis, a type of astrocytoma, would be likely to damage the seventh nerve from the beginning in association with unilateral brainstem signs. Though the situation of the disturbance is consistent with glioma pontis, its clinical course presents serious difficulties. First, it is evolving too rapidly to be consistent with the usual course of that tumor. There is the extraordinary remission of symptoms and signs in the month of August. Finally the early involvement of a group of cranial nerves with incomplete patchy lesion of brainstem makes one think more peripherally in the posterior fossa and less in terms of central disturbance.

Since the remission of signs was so striking, we might examine that part of the history more carefully. There was no evidence of recurrent meningeal disease, obstruction of venous sinuses, or other vascular disease. Although the child had improved quite rapidly from a state of deep stupor with embarrassment of all brainstem functions, left-sided ataxia was noted during the remission. Whether the child had had a bilateral cerebellar ataxia in the beginning and now that she improved the ataxia persisted more on the left side, or whether this was a new sign on the left side is difficult to determine. At all events rhythmic tremors in the left limbs became more obvious. The disorder of the seventh and eighth nerves improved, the weakness of the sixth nerve vanished, and the analgesia of the right face disappeared. The child presented residual left cerebellar signs and residual right cranial nerve palsy. After some three weeks there was a recurrence of vomiting without relation to meals, slurred speech, and somnolence. Obviously the process had again become active and again embarrassed the brainstem function. There was now slight papilledema, although the lumbar puncture still showed that the pressure was only 130 mm.; there was still no cellular reaction or protein increase in the spinal fluid. The findings on second admission indicate that

distortion of the brainstem had again occurred. This remarkable remission in a space-occupying lesion strongly suggests the presence of some kind of cystic process. Cerebellar cysts are particularly liable to such a remission. Whether this is because their size is altered by hydration and dehydration, or whether there is alternating necrosis and cyst formation, I do not know. For example, the hemangioblastomatous cyst of Lindau's disease in the cerebellum may be associated with sudden remission of symptoms for a period of many months. Is it possible that this patient had such a cyst? Hemangioblastoma most commonly occurs in the cerebellum but may bulge into the ventricle and compress the brainstem. In the present case, such a cyst would have to protrude laterally to affect predominantly the right side of brainstem and seventh and eighth cranial nerves without acute hydrocephalus. I have never seen one do that, but it is a possibility. Another possibility would be that we are here dealing with a gliomatous cerebellar cyst, but a cerebellar astrocytoma is not likely to be so laterally situated. Glioma pontis, which would satisfy the requirements of location of the lesion, is not a cystic tumor. It does not commonly undergo necrosis and cyst formation. We have, therefore, to choose between a type of pathology that fits the location of the process and another that more closely corresponds with its behavior. The striking remission leads me to the conclusion that there is a cystic degeneration of a neoplasm, most likely a hemangioblastomatous cyst of cerebellum, possibly glioma pontis.

DR. THOMAS W. FARMER: The patient had evidence of increased intracranial pressure as manifested by headache, vomiting, electroencephalographic changes, and digital markings. There were clear signs of involvement of the right fifth, sixth, seventh, and eighth cranial nerves, conjugate gaze palsy, horizontal and vertical nystagmus, bilateral pyramidal tract signs, and then later left cerebellar signs. This process had evolved over a period of two and a half months and terminated fatally. The remarkable feature is the striking remission. I concluded that this was a glioma in the pons, and that these acute changes with remission were related to some change in the tumor which I could not very well explain. I would not be certain whether this was due to a cystic tumor, but that would be the best possibility.

DR. TALBERT: I should like to thank the discussors for a stimulating and enlightening discussion of what was a difficult diagnostic problem. This patient was under the care of our neurosurgeon, Dr. Luther Martin, whose original diagnosis was intrinsic pontine tumor. Since it was not clear to us whether there was increased pressure and since the patient was febrile on admission, it was felt advisable to watch her for a few days before proceeding with operation or air studies. While we were thus temporizing, she began to improve, to our surprise. It was about then that the history of smallpox vaccination was obtained, and I pounced upon this as a possible etiologic factor. Our final diagnosis on the first admission was postvaccination encephalomyelitis – a rather naive diagnosis, I must admit. I explained away the lack of spinal fluid reaction by assuming it had subsided before the puncture was done. Certainly, the course at that time seemed that of a self-limited and regressing disease affecting the brainstem and cerebellar pathways. Then when the ultimate course finally declared itself, it was obvious how wrong our optimism had been and that Dr. Martin's original impression was most likely correct. The discussion today has brought out some possibilities not even considered by me in evaluating the case in the hospital. I think the point made by Dr. Denny-Brown that cystic lesions are capable of regressions to a degree is an important one.

PATHOLOGIC DISCUSSION

DR. MARGARET C. SWANTON: General inspection of the brain reveals that the lepto-

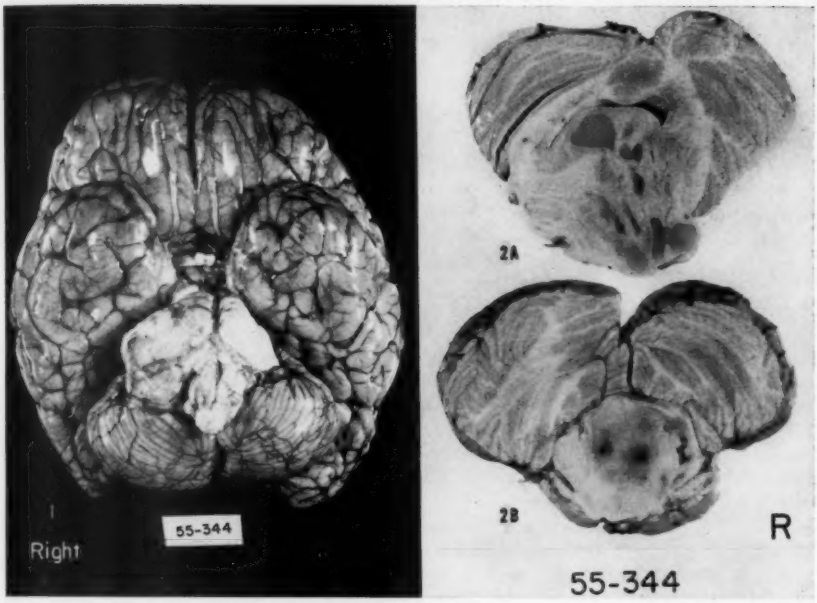

FIG. 1. Ventral surface of brain showing markedly asymmetric enlargement of pons and right cerebellar peduncles, and to lesser degree of upper medulla.

FIG. 2. *A.* Pons and cerebellum at level of brachia pontis, with replacement of tegmentum, right basilar pons, and brachium by multicystic neoplastic tissue. Basilar artery in groove on ventral surface indicates original midline of pons. *B.* Lower pons and cerebellum showing complete obliteration of internal architecture of pons by neoplastic tissue with focal necrosis and hemorrhage.

meninges are thin and transparent, with no gross evidence of hemorrhage or of inflammatory or neoplastic cellular infiltration. The circle of Willis and its major branches show no abnormality. The cerebral hemispheres are symmetric and uniformly normal in color and consistency. There is only very moderate flattening of gyri over the convexity, with concomitant narrowing of sulci. Very shallow grooves are present on the anterior ends of the hippocampal gyri, farther from the medial border on the right than on the left, due to asymmetry of the brainstem rather than of the cerebrum. On sectioning the cerebral hemispheres no gross abnormalities are seen. The lateral ventricles are only slightly and symmetrically dilated. The third ventricle is 6 millimeters wide. All of these findings indicate a real, but relatively small, degree of increase in supratentorial intracranial pressure, probably of little significance in itself in the demise of the patient.

The folia of the cerebellar hemispheres are moderately flattened. The cerebellum appears slightly asymmetric, more with respect to the shape than to the size of the hemispheres. Mediolateral and dorsoventral dimensions are normal bilaterally, but the anteroposterior dimension of the right hemisphere is 6 millimeters greater than that of the left. The right cerebellar peduncles are considerably enlarged. The only evidence of a cerebellar pressure cone is an obliquely oriented, 10 millimeter wide, shallow groove about 10 millimeters from the anterior border of the tonsil on the ventral surface of the right hemisphere.

In an examination of the brainstem, the ventral aspect of the midbrain and diencephalon shows no external abnormalities except for slight enlargement of the right cerebral peduncle. The pons, however, shows marked asymmetric enlargement (figure 1). The basilar artery is nearly buried in a ventral sulcus 3 to 4 millimeters deep. The broadest portion of the left basilar pons is 22 millimeters wide, and at the same level the right half is 33 millimeters wide. The pattern of transverse fiber tracts, which is externally visible on the left basilar pons, has been obliterated on the right, where there are several poorly demarcated, bulging, firm, pale nodules 10 to 15 millimeters in diameter. This enlargement involves the right cerebellar peduncles as well as the pons. The upper end of the medulla is moderately and somewhat asymmetrically enlarged, the transverse diameter at the level of the inferior olivary nuclei being 22 millimeters. This enlargement is not apparent below the level of the inferior olivary nuclei. At the posterior end of the fourth ventricle there are several conspicuous rounded elevations of the floor about 3 millimeters high, the one on the right being more prominent. From the depression in the floor just superior to these, the floor of the fourth ventricle arches upward toward the cerebellum instead of having its normal configuration.

Sectioning of the brainstem and cerebellum reveals that the superior end of the mesencephalon does not appear to be asymmetric and its cut surface has a normal pattern. The inferior end, however, is mildly asymmetric, with the ventral end of the aqueduct deviated slightly toward the left. The tissue appears slightly whiter than normal, with decreased sharpness of definition of tracts and nuclei. The upper pons is remarkably asymmetric, with the right half being 7 to 10 millimeters wider than the left. The tissue is paler and slightly softer on the right side and there is indistinctness of the normal structural markings. The transverse fiber tracts in the basilar portion of the right pons deviate dorsally as they pass laterally. There is apparent separation of these tracts so that the basilar portion of the pons measures 15 millimeters from tegmentum to ventral surface on the left and 22 millimeters on the right. In the tegmental portion of the right half of the pons, which forms almost the entire width of the 17 millimeter wide floor of the fourth ventricle at the level of the lower end of the brachium conjunctivum, there is complete obliteration of normal tracts and nuclei by slightly grayish translucent tissue in which there are three small cysts, the largest 7 by 3 millimeters in cross section, all containing a gelatinous, pale yellowish coagulum. At the level of the brachia pontis (figure 2A), the left basilar pons plus lower end of the brachium is 21 millimeters wide and the corresponding measurement on the right is 33 millimeters. There is complete obliteration of architecture of the entire tegmental portion and most of the right basilar portion of the pons by similar neoplastic tissue containing numerous and larger cysts. The alteration in color and texture of tissue, without cyst formation, extends up the right brachium pontis and probably into the slightly blurred dentate nucleus. The distortion of the brainstem at the level of the restiform bodies (figure 2B) is similar, except that the obliteration of surface landmarks is more complete and involves the left side to some degree. There is yellowish and dark reddish discoloration of focal softened areas in the tumor tissue at this level, as well as a few cysts. The tissue bulges upward into the fourth ventricle, which is still not quite completely obliterated. At the level of the inferior olivary nuclei, the medulla is asymmetric, the right half being 3 to 4 millimeters larger in all dimensions, with indistinct architectural pattern of its cut surface. The medulla just below the inferior olivary nuclei appears normal on gross examination of its cut surface. At no point does the neoplasm appear to have extended into the subarachnoid space.

Histologically, only the brainstem and

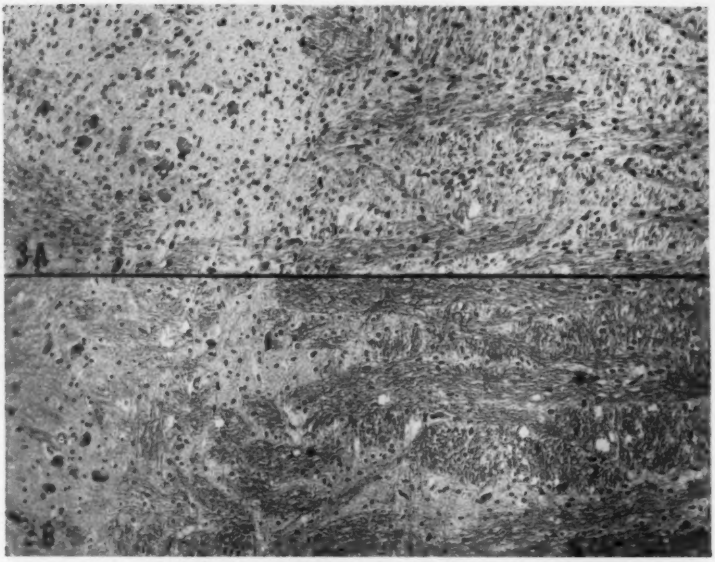

FIG. 3. Corresponding fields in upper basilar pons. *A*. Infiltration by small tumor cells with minimal damage to myelin sheaths. *B*. Normal pons for contrast. Hematoxylin and eosin stain. x 100.

cerebellum are unusual. The total microscopic extent of this neoplasm is from upper right cerebral peduncle to right ventrolateral medulla at the level of the lower third of the inferior olivary nucleus, and laterally via the brachium pontis into the right dentate nucleus. At these extremities, there is only an infiltration of preexisting tracts and nuclei by very moderate numbers of small neoplastic cells, without significant damage to neurons or myelin sheaths. In many areas this simulates isomorphous gliosis. These cells are small, with round to oval nuclei of astrocytic type but with more or less increase in content and size of chromatin aggregations. Many lack stainable cytoplasm, but about half are gemastocytic astrocytes. As one approaches the pons, tumor cells become more numerous, with wider separation of and gradually increasing damage to neurons and myelin sheaths in portions of the right side (figure 3). This infiltration with relatively little destruction explains readily the clinical impression of limitation of the tumor to the pons.

In the midpons, with its extensive and cystic tumor that is bilateral in the tegmentum (figure 2A), the neoplastic tissue densely infiltrates preexisting structures and completely replaces many of them. It is moderately cellular, with cells of variable shape, chromaticity, and arrangement, but all of relatively small size, associated with abundant glial fibrils. No mitotic figures are identifiable. Large fields have the appearance of gemastocytic astrocytoma (figure 4). These merge into areas of astrocytes with very little cytoplasm. There are all gradations from these to cells with characteristics of polar spongioblasts, arranged in some places to form bundles of the fairly coarse fibrils extending from one or both ends of their slender cell bodies (figure 5). Where cysts are present, there are varying degrees of edema of the tissue with transition to discrete collections of fluid (figure 6).

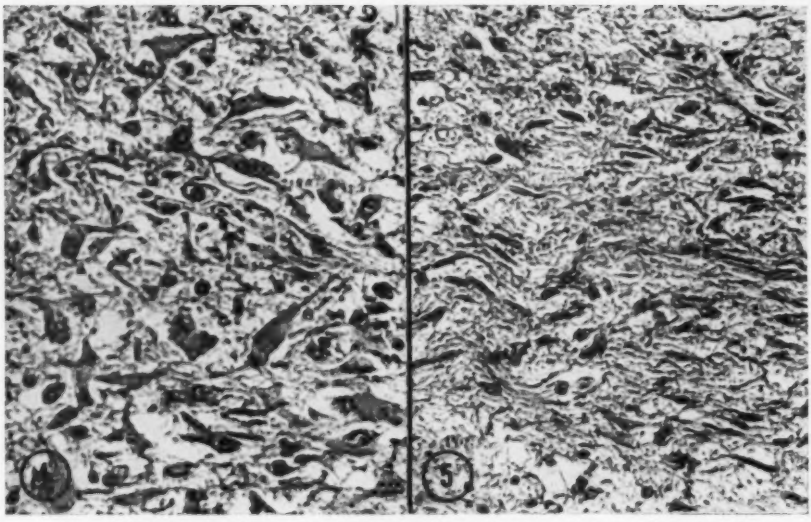

FIG. 4. Midpons. Neoplasm with characteristics of gemastocytic astrocytoma. Phosphotungstic acid hematoxylin stain. x 450.
FIG. 5. Midpons. Neoplasms with characteristics of spongioblastoma polare. Phosphotungstic acid hematoxylin stain. x 450.

It is thus evident that this tumor is a brainstem glioma, with characteristics of an astrocytoma merging into spongioblastoma polare. The histology is further varied by the presence of areas of conspicuous vascularity, with marked endothelial and adventitial cell proliferation (figure 7). Recent thromboses in groups of these vessels are associated with the bilateral, multiple, small areas of necrosis and hemorrhage in the lower pons (figure 2B), about which tumor cells tend to show a "palisading" arrangement. These are characteristics of glioblastoma multiforme. The cellular evidence of greater anaplasia in these areas is limited to somewhat more hyperchromaticity and variation in nuclear size and shape, occurring in small cells with very rare mitotic figures, and only occasional bi- or trinucleation. Glial fibrils are still abundant. One would have to classify this portion of the tumor as glioblastoma multiforme, although the cells are not so anaplastic and bizarre as those traditionally associated with this type of glioma.

This lack of uniformity in degree of cellular differentiation is more common in gliomas than would be suspected from a traditional nomenclature emphasizing single cell types. It is quite analogous to findings in neoplasms of other tissues, and makes a simplified terminology based, where possible, upon degree of anaplasia of cell types normally present seem more related to reality. According to Kernohan's classification,[1] this glioma would be called astrocytoma, grade III in the lower pons and grade II elsewhere. This is more consistent with the observed transitions from one degree of anaplasia to another than are multiple "cell-type" designations. It is certainly more consistent with the concepts and terminology of neoplasms of other tissues than is a device such as that proposed by Pilcher.[2] Using spongioblastoma polare as an inclusive term, he called those tumors with con-

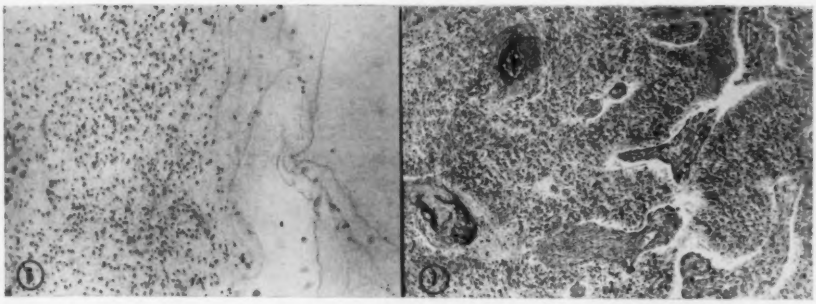

FIG. 6. Midpons. Edematous neoplastic tissue (left) and cyst (right). Hematoxylin and eosin stain. x 100.

FIG. 7. Lower pons. Small tumor cells with moderate pleomorphism. Numerous blood vessels with hyperplastic endothelial and adventitial cells showing recent thrombosis (left). Phosphotungstic acid hematoxylin stain. x 100.

spicuous astrocytomatous elements the "mature type," more homogeneous ones the "pure type," and those with pleomorphism and giant cells the "primitive type."

In this case, fairly well differentiated astrocytoma is the quantitatively predominant tissue, with polar spongioblastoma second. Cyst formation is a relatively common slow degenerative change in the former elsewhere but not in the brainstem. It is not so uncommon in polar spongioblastomas of the brainstem, however. Development of these cysts and fluctuation in their size and in the edema of the surrounding tissue may have been accentuated in this case by close proximity to areas with abnormal, hyperplastic, small vessels. The visible fibrin threads in the fluid and its grossly gelatinous consistency suggest vascular exudation of protein-rich fluid as a contributory factor. Changes in these same vessels, which are not present in pure astrocytomas, clearly led to necrosis in the least well diflerentiated portion, or glioblastoma multiforme. The thrombi in groups of these vessels, and many of the necrotic areas appear histologically to be of relatively recent origin. Swelling resulting from these changes may well have been an important terminal factor.

In summary, this five year old girl with a two and a half month history of neurologic disorder had a glioma of the brainstem, largest and most destructive and least well differentiated in the pons, but infiltrating the right side of the mesencephalon, upper medulla, and brachium pontis. In the lower pons it would have to be classified as glioblastoma multiforme (astrocytoma, grade III),[1] and elsewhere it runs the gamut of fairly well differentiated astrocytoma, often predominantly gemastocytic, to spongioblastoma polare (all included in astrocytoma, grade II).[1] Its pattern of growth above and below the pons, which is typical of brainstem gliomas, is ample explanation for the clinical evidence of its limitation to the pons. As Dr. Denny-Brown surmised, hydrocephalus was not of critical degree, but enlargement and distortion of tissue within the confines of the posterior fossa were severe. Surprisingly frequently in pontine gliomas, the slit-like fourth ventricle such as seen in this case appears adequate to prevent more than mild to moderate internal hydrocephalus. The distribution of the tumor with maximal damage in the right pons, but with bilateral involvement, provides an anatomic basis for the cranial nerve, pyramidal tract, and cerebellar system deficits. The dilemma facing our discussor in having to choose between a type of pathology that fits the location of the process and another that more closely corresponds with its behavior (i. e., the strik-

ing remission) is resolved by the discovery that this neoplasm is, in fact, one of the brainstem gliomas with cysts of significant size. These are more likely to be seen in polar spongioblastomas than in pure astrocytomas in this location, which helps to explain their presence in this case. The glioblastoma multiforme component in this tumor in a young child is less startling when one reviews some of the reported series of brainstem gliomas[3–6] and finds 30 to 35 per cent of those in children to be of this type, despite the rarity of supratentorial glioblastoma in this age group. The results of vascular occlusion in this portion of the tumor were probably significant in hastening the onset of the time at which gradually increasing posterior fossa pressure and replacement of pontine tissue became incompatible with life.

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■ Taking as true for a moment the old view that the spinal cord contains nerve-fibres, which are the continuation of those of the posterior roots and of the nerves of the sensitive parts of the body, and possessing the same properties in this nervous centre as in these roots and nerves, what ought to be the result of pressure on this organ? According to the seat of the pressure, there ought to be a pain felt as if it originated from a more or less considerable part of the body. We have read carefully the details of a great many cases of fracture or luxation of the spine, or of tumors pressuring upon the spinal cord; we have also carefully questioned many patients, and we can state that the referring to the periphery is rare, and that it never exists unless the posterior roots are irritated or the spinal cord inflamed.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Myasthenia Gravis with Features Resembling Muscular Dystrophy

Lewis P. Rowland, M.D. and Alfredo N. Eskenazi, M.D.

MYASTHENIA GRAVIS has been regarded traditionally as a disease of the myoneural junction, in which the muscles show no alteration other than the presence of small collections of lymphocytes. In recent years, however, it has been shown that a significant number of patients with clinical syndromes typical of myasthenia gravis have histologic lesions of striate and cardiac muscle. Several authors[1–4] have described necrosis of muscle fibers and an inflammatory cellular reaction consisting of mononuclear and polymorphonuclear cells, eosinophiles, and occasionally giant cells. This reaction may be identical with that found in polymyositis. These cases suggest that, in some patients at least, the pathophysiology of myasthenia may involve muscle as well as, or instead of, the neuromyal junction.

Further evidence for this hypothesis is afforded by occasional reports of patients with myasthenia gravis who have features suggestive of muscular dystrophy.[6–10] It is possible that this association is fortuitous, since myasthenia may occur concomitantly with many seemingly unrelated disorders.

However, some muscular atrophy is encountered often enough in patients with myasthenia to suggest that myopathic features should not be disregarded. The exact incidence of atrophy in myasthenia has not been stressed in the reports of large series of cases since the introduction of neostigmine, but Merritt[11] cited a figure of approximately 10 per cent and isolated cases have been recorded.[12–15] In a recent series of fatal cases, clinically detectable wasting of shoulder girdle muscles was recorded in three of 39 patients.[16] When the clinical similarity to muscular dystrophy is striking, as in the following case, consideration of myopathy is necessary.

CASE HISTORY

A 38 year old woman was admitted to Montefiore Hospital for the second time in 1954 because of difficulty in walking and weakness of the arms since early childhood. There was no family history of similar disorder.

Her birth was normal and the neonatal period uncomplicated. No abnormality was noted by her parents until she started to walk at the age of 15 months. She always had difficulty in walking without assistance and fell frequently. She was never able to participate in the active exercises of her friends. She had never been able to move her eyes as long as her parents could remember, but they could not recall whether the difficulty was present during the first year of life. When she was eight years old

From the division of neurology, Montefiore Hospital, and the department of neurology, Columbia University College of Physicians and Surgeons, New York City.

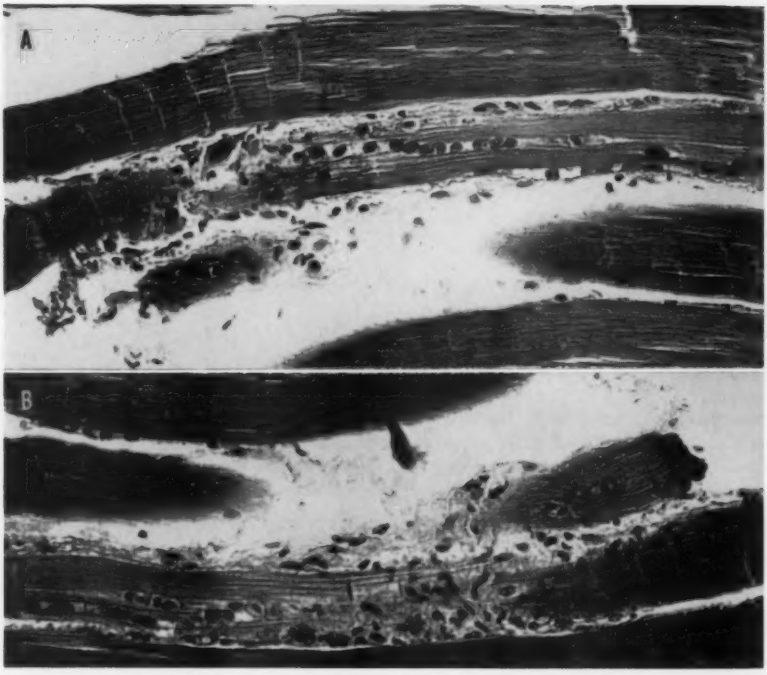

FIG. 1. *A* and *B*. Photomicrographs of skeletal muscle biopsy (1951) showing focal areas of muscle degeneration and sarcolemmal nuclear proliferation.

she was admitted to another hospital and a diagnosis of "Oppenheim's disease" was made. In adolescence she improved somewhat and was able to go to school. For a while she did secretarial work, but she had difficulty in traveling because of the long flights of stairs in subway stations.

She married at age 28 and subsequently delivered two children. During each of the pregnancies her strength improved considerably, but she relapsed in the puerperium each time.

In 1951, at the age of 34, she was admitted to Montefiore Hospital for the first time. She was given 1.0 mg. neostigmine parenterally, but there was no increase in strength and she complained of abdominal cramps. Urinary creatine excretion was 816 mg. in 24 hours; creatinine, 1.241 gm. A muscle biopsy showed a few foci of muscle degeneration and sarcolemmal nuclear proliferation (figure 1) which were compatible with the diagnosis of muscular dystrophy. Electric reactions of the muscles were normal. Cortisone and ACTH were administered in one week trials without effect.

In 1954 she was readmitted because of increased weakness during the preceding months. She had to use a cane for walking, and weakness of the arms interfered with her ability to care for her children. Ocular immobility and ptosis of the eyelids persisted, but she rarely had dysphagia and never experienced dysarthria or dyspnea.

Examination. General physical examination was unremarkable except for slight obesity and marked accentuation of lumbar lordosis (figure 2). There was marked ptosis of both eyelids. Lateral movements of the eyes were almost absent and she was completely unable to look up, although downward movements were good. She was unable to close the eyes completely, whistle, or retract the corners of the mouth in smiling. The pupils and optic fundi were normal and there was no weakness of the jaws, uvula, or pharynx. There was no

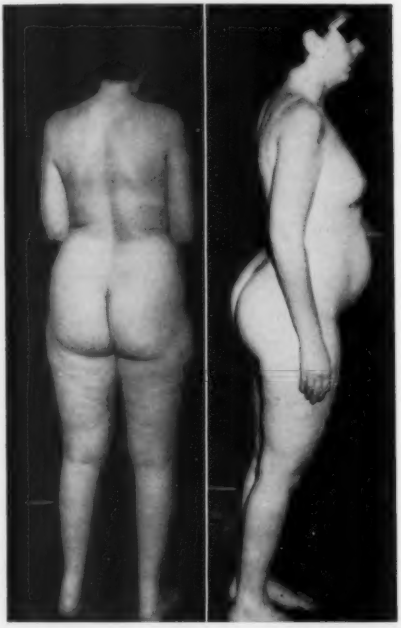

FIG. 2. General habitus and marked lordosis.

dysarthria. Weakness of anterior flexion of the neck against resistance was observed, but lateral turning was unimpaired and there was no sternomastoid atrophy. The upper trapezius was normal.

There was no winging of the scapulae and the shoulder depressors were strong, but she was not able to raise her arms to shoulder level. Diffuse weakness throughout the arms and hands was detected when resistance was offered, although she could move all muscles through full range against gravity; this was most marked proximally.

There was marked weakness of the muscles of the pelvic girdle and she was unable to flex the hips completely in a sitting position or rise from supine or squatting positions. Her gait was "waddling" in character and she required a cane for support. The quadriceps, anterior tibialis, peroneal, gastrocnemius, and posterior tibialis muscles showed no weakness.

There was no definite atrophy, although the muscles semed flabby and soft. There were no contractures, pseudohypertrophy, or myotonic phenomena. Tendon reflexes were active and equal everywhere. Plantar responses and sensation were normal.

Laboratory data. Roentgen examination of the mediastinum revealed no evidence of thymoma. Soft tissue films of the extremities showed an increased amount of subcutaneous tissue. Urinary creatine excretion was 1.5 gm. in 24 hours; creatinine, 1.2 gm. Radioiodine uptake was 38 per cent in 24 hours.

Therapeutic tests. In response to Tensilon (10 mg. intravenously) or neostigmine (1.5 mg. subcutaneously or 0.5 mg. intravenously), she showed consistent improvement in ptosis and ocular motility on several occasions (figure 3). In addition, strength of arm and leg muscles improved dramatically. She was able to raise her arms overhead and discarded her cane (although she still "waddled").

Provocative test. After appropriate precautionary measures in case of respiratory emergency, she was given 0.3 mg. d-tubocurare intravenously (1/20 of the calculated curarizing dose for a normal person of her weight). There was immediate and complete paralysis of the extremities and neck and she was aphonic. Respiratory excursions of the thorax diminished, but she had no dyspnea. These symptoms were gradually corrected by the administration of 2.0 mg. neostigmine and 10 mg. Tensilon intravenously.

Subsequent course. On oral therapy with neostigmine and pyridostigmine (Mestinon) she

FIG. 3. *A.* Marked ptosis and inability to move eyes laterally. *B* and *C* thirty seconds after 10 mg. Tensilon intravenously, ptosis had receded considerably and some lateral movement was possible, to the left *B* and to the right *C*.

has noticed considerable increase in strength. She is able to walk without assistance, carry her children, and assist in housework, but she is still partially incapacitated.

DISCUSSION

The features in this case reminiscent of muscular dystrophy are: 1) the distribution of weakness, most pronounced in the shoulder and pelvic girdles and trunk, resulting in characteristic waddling gait, lordosis, and inability to rise from supine or squatting positions; 2) the heavy creatinuria; and 3) the muscle biopsy.

On the other hand there are several features of this illness which are atypical for muscular dystrophy: 1) the absence of more marked wasting, contractures, or disability after so many years of illness; 2) the presence of almost complete ophthalmoplegia from the onset; and 3) the preservation of tendon reflexes.

The striking response to Tensilon and neostigmine and the marked sensitivity to curare establish this as a case of myasthenia gravis. In view of the features enumerated above which are atypical for muscular dystrophy, it might be considered that only myasthenia was present. Lordosis[17] and creatinuria[18] sometimes occur in myasthenia and the histologic changes in the specimen examined were not widespread. Still, these are features of dystrophy, and the striking resemblance this woman bears to patients who have progressive muscular dystrophy may be more than superficial.

Walton and Nattrass[8] suggested that disorders of this nature should be classified as "myasthenic myopathy," while the term "myasthenia with polymyositis" has been suggested for cases in which inflammatory lesions exist in skeletal muscle.[19] Subdivisions of this nature may be helpful in studying the natural history of myasthenia and in providing clues for investigation, but these distinctions may be artificial; "myopathy," "polymyositis," and "myasthenia" are all products of unknown pathophysiologic processes.

The possible importance of cases such as this seems to be twofold. First, patients who apparently have atypical myopathies may benefit from the administration of neostigmine. Second, it is suggested that investigations into the nature and pathogenesis of myasthenia gravis should be concerned with the muscle itself as well as the neuromuscular junction.

SUMMARY

A case history is described of a patient with a muscular disorder which resembled muscular dystrophy in several respects but was atypical in others. She improved dramatically after the administration of Tensilon and neostigmine and showed exquisite sensitivity to curare, thus establishing the presence of myasthenia gravis. The significance of this case is discussed in relation to the possible importance of myopathy in the pathogenesis of some cases of myasthenia gravis.

The author is indebted to Dr. M. G. Netsky for his interpretation of the biopsy specimens in this case, and to Mr. Antol Herskovitz for preparation of the illustrations.

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■ *What is the channel of the nervous irritation generated when the anterior roots are excited?* In the first place, we think it is necessary to repeat, that the current is not towards the spinal cord, inasmuch as Magendie has well proved that after the section of the anterior roots of a spinal nerve, we may irritate the central part without causing the least manifestation of any kind of sensation. It results, therefore, and as positively as possible, that the anterior roots have not the property of sensibility in the same manner as the really sensitive parts. On the contrary, pain is caused by the irritation of the parts of the anterior roots in appearance separated from the nervous centres. But if the trunk of the nerve is divided, the irritation of the anterior roots on either end remains completely painless; it results, therefore, that the current which causes the pain passes the trunk. But how far does the current extend towards the periphery of the body, before returning upon itself in order to reach the spinal cord and the sensorium? This has not been positively determined. It seems, however, already, from the experiments of Magendie, of Professor Cl. Bernard, of Volkmann, of Schiff, and from my own, that the return takes place at the peripheric extremity of the nerve-fibers. Kronenberg and Pappenheim have erroneously admitted that the current merely passes from the anterior roots to the posterior, at the place where they meet to form the trunk of the spinal nerves.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Sydenham's Chorea

A Clinicopathologic Study

Henry S. Colony, M.D. and Nathan Malamud, M.D.

THE LITERATURE concerning the pathology of Sydenham's chorea is meager. Since the disease is rarely fatal, there has been little opportunity to study the pathologic process.

The following case is presented, with a brief summary of the literature, in the hope that it will throw some light on the condition.

REPORT OF A CASE

A 21 year old white male was admitted to the U. S. Naval Hospital, Oakland, California, with a diagnosis of anxiety reaction. He had been well until three months before admission when he began acting peculiarly. Whereas he was formerly easy-going and sociable, he now became withdrawn, silent, and appeared tense and rigid. When relaxed he had spontaneous purposeless movements of his extremities, and speech was unintelligible.

On admission to the hospital his condition was first considered to be emotional in origin, since he appeared to be nervous and negativistic. Subsequently, however, it was noted that there was considerable involuntary facial grimacing, speech was explosive and unintelligible, and there were unsustained abrupt choreiform movements of all extremities. Hypotonus was demonstrable and there was a tendency to over pronation of the hands. There were no changes in the cranial nerves, deep reflexes, or sensory system. A soft, blowing, systolic murmur was heard in the mitral area of the heart, but a series of three electrocardiograms were within normal limits. Electroencephalograms were grossly abnormal, with complete absence of any basic rhythm. Tracings were characterized by random one-half to three per second activity throughout, initially most marked in the left frontotemporal area, but gradually becoming more generalized.

The white blood count was 6,400 per cu. mm., with 61 per cent neutrophils, 29 per cent lymphocytes, 5 per cent monocytes, and 5 per cent eosinophils. The red blood count was 4,480,000 per cu. mm., with 13 gm. hemoglobin. Kahn test of the blood was negative. Blood sedimentation rate was 8 mm. per hour; hematocrit was 47 packed cell volume. A spinal fluid examination on admission revealed 2 white blood cells per cu. mm., negative colloidal gold, and negative Kolmer reactions. A repeat spinal fluid examination several weeks later disclosed the same findings, with the exception of 100 mg. per cent of total protein, but a negative Pandy reaction. Agglutination studies for Western Equine, St. Louis, mumps, and herpes encephalitis were all negative. Cultures of the spinal fluid revealed no growth. Porphyrin studies were negative. The serum calcium was 9.7 mg.; inorganic phosphorus was 3.2 mg. per cent. A blood copper level was 69 gamma per 100 cc. Liver function studies were normal. Serum protein was 6.5 gm. per cent, albumin was 3.6, and globulin 2.9 with an A/G ratio of 1.2. An antistreptolysin titer was greater than 166 Todd units. Roentgenograms of the chest, spine, and skull were negative.

From the U. S. Naval Hospital, Oakland, California. The statements and conclusions of the authors are the result of their own study and do not necessarily reflect the policy or opinion of the United States Armed Forces.

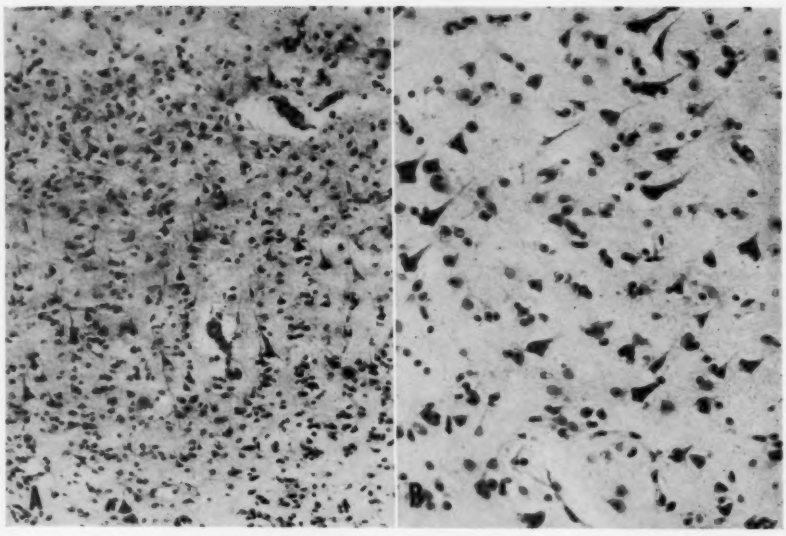

FIG. 1. Cerebral cortex showing diffuse dropping out and hyperchromatosis of neurons. *A*. Nissl method, x 100. *B*. Same with reactive proliferation of glial nuclei. Nissl method, x 200.

A diagnosis of Sydenham's chorea was made, and cortisone therapy was instituted and continued for a two week period. Since there were no beneficial effects, cortisone was discontinued, and the patient was given a two week course of ACTH therapy without benefit. During his stay in the hospital he had a steady downhill course. He developed a marked intention tremor and at times the movements were so gross as to resemble ballismus. He became confused, disoriented, and reacted to auditory hallucinations. On the 106th hospital day he died of respiratory paralysis.

Necropsy

The only findings in the internal organs were hydropericardium, pulmonary edema, and passive congestion of the viscera. The brain weighed 1,520 gm. and showed a patchy atrophy of the cerebral cortex.

Microscopically, in all areas of the brain examined, there was widespread degeneration of neurons which varied only in degree.

In the cerebral cortex a diffuse dropping out of nerve cells was noticeable in all layers, resulting in their being crowded together in a mild disturbance of the cytoarchitecture (figure 1A). The remaining neurons showed hyperchromatosis and shrinkage, surrounded by increase in satellite oligodendroglia and more particularly by a marked proliferation of astrocytic nuclei (figure 1B). These could be demonstrated in Cajal preparations as branching forms with short processes which were partly attached to walls of blood vessels (figures 2A and B). In some areas there was a laminar spongy degeneration in the molecular layer of the cortex (figure 3A). Nowhere was there any evidence of inflammatory reaction such as round cell infiltration or microglial response, nor any sign of occlusion of blood vessels.

In the cerebral cortex the process was severe in the frontal and temporal lobes, somewhat less so in the parietal, occipital, and motor areas. The thalamus (figure 3B) was severely involved, particularly in its nuclei ventralis anterior, dorsomedialis, and pulvinar. The caudate and putamen nuclei were moderately affected, while only mild changes were encountered in the globus pallidus, red nucleus, subthalamic body, substantia nigra, hypothalamus, dentate nucleus, cerebellar grey matter, and brainstem.

COMMENT

In the literature dealing with the pathology of Sydenham's chorea, three different

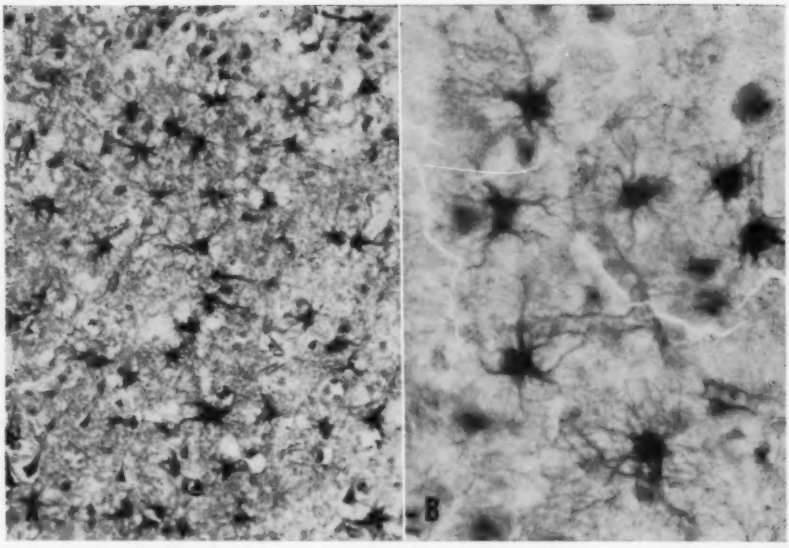

FIG. 2. Diffuse proliferation of astrocytes in cerebral cortex. Cajal's gold sublimate method. *A.* x 170. *B.* x 475.

types of lesions have been reported: 1) inflammatory, 2) degenerative, and 3) vascular.

In the cases first reported by Tretiakoff[1] and by Marie and Tretiakoff,[2] inflammatory changes were described which were considered identical with the findings in epidemic encephalitis. Greenfield and Wolfsohn[3] also noted inflammatory lesions, but felt that chorea was a meningoencephalitis of rheumatic origin.

Lewy,[4] in an extensive report on 11 cases, could find signs of inflammation in only one case, the remaining showing predominantly toxidegenerative changes. Ziegler[5] and Gordon and Norman[6] also emphasized the degenerative changes in their cases.

Lhermitte and Pagniez,[7] followed by van Bogaert and Bertrand,[8] sought to distinguish two types of chorea, an inflammatory and a degenerative form. Van Gehuchten[9] attempted to bridge this gap by considering the two types as merely acute and subacute phases of the same disease.

Von Santha[10] described chronic vascular lesions in his case similar to the endarteritic changes seen in rheumatic "encephalitis." McCulloch[11] expressed the opinion that Sydenham's chorea resembled more closely the acute exudative than the chronic proliferative forms of rheumatic fever. In the same category might be considered the recent observations of Bauer and co-workers[12] and of Glaser,[13] who studied cases of disseminated lupus erythematosus with clinical features of Sydenham's chorea and found the specific vascular lesions of lupus within the central nervous system.

Lehoczky[14] found a combination of inflammatory, degenerative, and vascular lesions in his three cases and saw no justification for distinguishing different types.

In our case, a subacute diffuse degenerative change without inflammatory or vascular components was the exclusive finding. Clinically it was a classic case of chorea. There were, however, no signs or history of rheumatic fever and the sedimentation rate

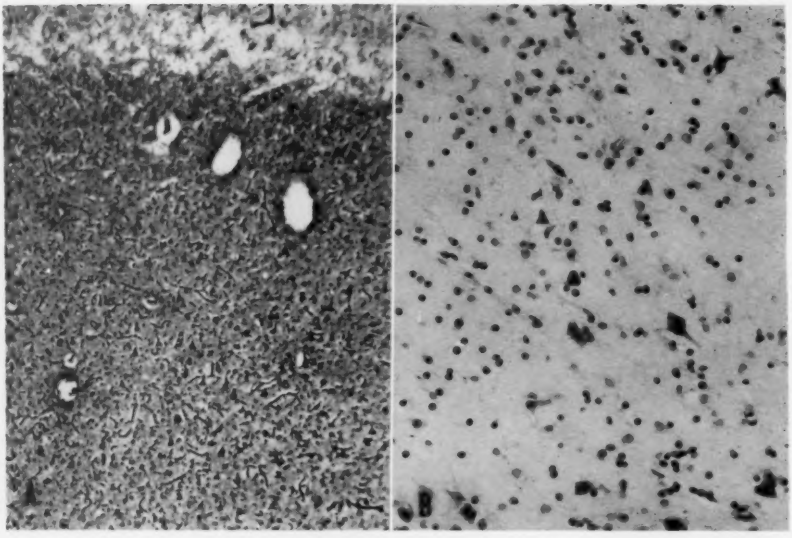

FIG. 3. *A.* Cerebral cortex showing spongy degeneration in molecular layer. Hortega's silver carbonate method, x 45. *B.* Thalamus showing dropping out of neurons and proliferation of glia. Nissle method, x 200.

was normal. In recent years, Kagan and co-workers[15] reported on a large series of cases of Sydenham's chorea not associated with rheumatic fever and having normal sedimentation rates, which the authors designated as cases of "chorea, cause undetermined."

After surveying the literature, one is forced to the conclusion that Sydenham's chorea is not an entity, but a syndrome of such diverse conditions as rheumatic fever, disseminated lupus erythematosus, encephalitis, and certain toxi-degenerative conditions of undetermined etiology. The pathology varies in accordance with the given disorder.

The question of the anatomic site of the lesions responsible for the choreic symptomatology has remained unsolved. Almost all authors dealing with the subject find it impossible to attribute the syndrome to a precise localization, since the changes are invariably diffuse. In all reported cases, the cerebral cortex was affected along with the striatum and other extrapyramidal nuclei. Our case was no exception and, in fact, showed more severe pathology in the cortex and thalamus than in the so-called extrapyramidal system.

SUMMARY

1. A case of Sydenham's chorea not associated with any manifestations of rheumatic fever is reported clinically and pathologically.

2. The changes in the central nervous system were of an exclusively degenerative type.

3. The literature is surveyed and the opinion is advanced that Sydenham's chorea is not a disease entity, but a syndrome of many different disease processes.

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■ In the upper part of the cervical region of the spinal cord, near the crossing of the anterior pyramids, the results of experiments on the various parts of the spinal cord are very different from those of the same experiments in the dorsal region. In that part of the cervical region it is the section of the lateral columns, and of the part of the gray matter placed between the anterior and the lateral columns, which produces the most decided effect on voluntary movements, viz., a complete paralysis. The section of the anterior columns alone, when it has been made without a notable injury of the neighboring parts, causes a diminution of voluntary movements, which is by far not so considerable as after a section of these columns in the dorsal region. The section of the posterior columns and of the posterior parts of the gray matter in the cervical region hardly causes a diminution in the energy of the voluntary movements. From these results we conclude that in the upper part of the cervical region of the spinal cord, near the medulla oblongata, most of the conductors of the orders of the will to muscles are in the lateral columns and in the gray matter between these and the anterior columns.

C. E. Brown-Séquard in *Lectures on the Physiology and Pathology of the Central Nervous System*, published in 1860.

CASE REPORT

Thrombosis of the Internal Carotid in a Child

Fernando Cabieses, M.D. and C. Saldias, M.D.

THROMBOSIS of the internal carotid artery has received considerable attention in recent neurologic literature. Most of the reported cases, however, deal with patients whose age varied between 25 and 60 years, the incidence of this entity in childhood apparently being very low. Therefore, the description of this case is of general interest for neurologists and pediatricians.

A nine year old white boy without any relevant previous history was brought to the outpatient department on January 26, 1955 with the chief complaint of weakness of the right side of his body. Two days before, without prodromal symptoms, the child came home from school complaining of general malaise, nausea, and vomiting. His mother noticed awkwardness in the movements of his right hand and inability to hold a pencil and write. Because the boy had had an argument with an older person at school and appeared frightened, his parents disregarded his complaints until the following day when they noticed that the entire right side of his body appeared to be definitely weaker. He exhibited some difficulty in talking, and his temperature had risen to 38° C.

He was admitted to the hospital, where clinical examination showed a well developed alert youngster with apparently normal mental function.

The tendon reflexes were decreased bilaterally. The right abdominal reflex was absent and a positive Babinski sign was elicited on the right. The cooperation of the patient permitted a careful sensory examination which was completely negative. The eyegrounds had a normal appearance, there was no neck rigidity, and the remainder of the neurologic and physical examination was essentially normal.

Except for a slight elevation of the white blood count (9,500), routine laboratory analyses were within normal limits. Plain skull films, cerebrospinal fluid examination, and an electroencephalograph were also considered normal.

The day following admission, the neurologic signs were increased; complete right hemiplegia had developed, and hypesthesia for touch and pain had appeared on the right side of the body. On January 28 a pneumoencephalogram was performed under general anesthesia. The films showed a normal ventricular system (figure 1). In view of this, an arteriogram was performed by the open method two days later. The injection was made a few cm. below the bifurcation of the carotid. The films (figure 2) showed lack of filling of the internal carotid, with excellent filling of the external carotid. The wound was enlarged upward and the bifurcation was exposed. In this fashion by direct vision and by palpation, the first 2 cm. of the internal carotid artery was found to be pulseless and indurated. Thus, the diagnosis of thrombosis of the internal carotid artery was

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The opinions expressed in this paper are those of the authors and do not necessarily represent the views of the Bureau of Medicine and Surgery, Peruvian Navy.

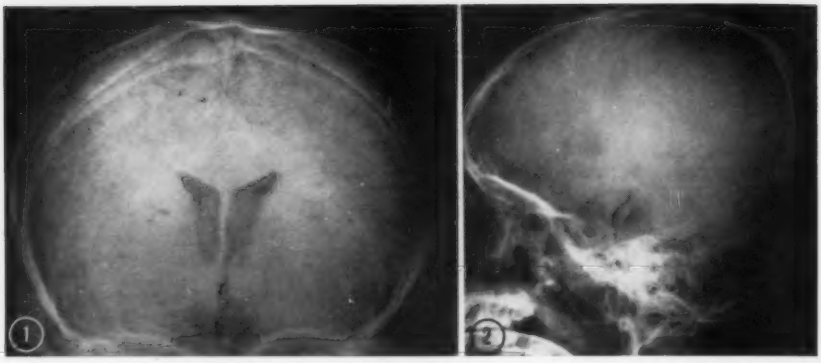

FIG. 1. Ventriculogram showing a normal ventricular system.
FIG. 2. Left common carotid arteriogram showing lack of filling of the internal carotid artery.

established. It was not considered advisable to perform any radical surgical procedure on the diseased vessel and the wound was closed.

Anticoagulant (Tromexan) and vasodilator (Papaverin) therapy was instituted. During the following ten days, no change of the neurologic picture was noticed. Thereafter, however, the motor symptoms began to improve very slowly and speech difficulties became less noticeable. Recovery was aided by a program of rehabilitation. Fifty days after admission the patient was walking and able to leave the hospital. The weakness of the arm and hand disappeared somewhat more slowly, but six months after discharge he was able to write normally and the neurologic examination was essentially negative.

SUMMARY

A case of thrombosis of the internal carotid artery in the neck in a nine year old boy is presented. The patient presented complete right hemiplegia, with speech disturbances. The diagnosis was established by open method arteriography, with direct visualization and palpation of the diseased vessel. It was not possible to determine the etiology. The patient recovered completely under conservative treatment.

Neurology

BOOK REVIEWS

Clinical Studies in Neurology

Harry Lee Parker, M.D. 1956. Springfield, Illinois: Charles C Thomas, Publisher. 364 pages. $6.50.

THIS IS NOT A TEXTBOOK in the usual sense: it is an experience; at least the reading of it is an experience out of the ordinary. This text reads like fiction, but it is packed with factual neurology in which romance, humor, pathos, philosophy, poetry, and history have been woven into the scientific warp. The scene of these medical dramas (or classes) takes place weekly in the wards of the Richmond Hospital, one of the oldest and largest in Dublin. The actors in the drama are patients, usually indigent, often bribed or inveigled into their roles by the charm of the star performer (and teacher) Harry Lee Parker, then chairman of the department of neurology at his alma mater, Trinity College, Dublin. The audience consisted of fourth year medical students and postgraduates from medical schools of Dublin who paid for the privilege of attending these sessions. Each performer in these medical dramas was a patient who illustrated a common neurologic problem. The real drama was furnished by the author who was deliberately informal and drove home his lessons through the use of colorful descriptive language abounding in metaphor and allegory, spiced by literary and historical references. Historic figures in neurology were introduced not merely by the dried facts pertaining to their contributions, but by anecdote, these fathers of neurology became personalities.

In the same manner each patient or actor in the drama is presented as a personality with a disorder and not just a case. Throughout these clinic sessions one feels the warmth and compassion of the physician-teacher. One sees, feels, and even smells the scene and the patient.

For Dr. Parker's students each class period must have been an unforgettable experience, with each disorder so etched upon the mind there could scarcely be need for recourse to notes or texts. One could surely not forget his telling description of causalgia: Speaking of patient, Bartholomew, who had received his median nerve injury while neutering a pig(!)—How he "resumes his previous posture of his hand held close to his belly, like a poker player with four aces. He has not however the same expression. His is that of a dying, disease riddled duck, alone in a rain-spouting thunderstorm, full of misery, madness and death."

One might mistakenly think this is not a scientific text. On the contrary, each neurologic disorder is completely discussed with anatomic and physiologic data, methods of diagnosis, causation, and current methods of treatment. The students participate in the examination of the patients, witness the performance of spinal punctures, see the results of electroencephalograms, angiograms, myelograms, and pneumograms. And just as important they wit-

ness the humaneness of the physician in neurologic practice.

Clinical Studies in Neurology is not a complete text in neurology; it was not the author's intention to make it so. It is intended to bring to the student that which constitutes the every day practice of medicine in neurology. It is unique as a literary production, almost completely lacking in medical jargon, proof that gobbledegook in medical writing is wholly unnecessary, that text need not be dull and formal to be instructive. It is bedside teaching at its best and should be required reading for every fourth year medical student. Any physician will find it entertaining and rewarding.

The reviewer, finding it an unusual book, read every word from beginning to end and commends it to all teachers of medicine, not only for the context but for the method and as an excellent example of patient-physician and student-teacher relationships.

Note: Dr. Parker had been a member of the section on neurology at the Mayo Clinic for 15 years before being called to the chair of neurology at Trinity College in Dublin in 1934. At the close of the war he returned to this country and to his former post where he is professor of neurology, Mayo Foundation, Graduate School, University of Minnesota.

M.G.M.

Grosse Nervenaerzte: 21 Lebensbilder

Edited by K. Kolle. 1956. Stuttgart: Georgthieme Verlag. 284 pages.

TWENTY-ONE SKETCHES of the life and achievement of leaders in neuropsychiatry written by 19 contributors comprise this volume. The selection is obviously somewhat arbitrary, although care was taken to consider the international scene. In some of the contributions the anecdote seems to this reviewer too prevalent. Even this small volume gives the reader some idea of the broad area which is involved. Of course, the present volume cannot compete with the wealth of information contained in Haymaker's *Founders of Neurology* (1953).

E. G.

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1. Fazekas, J.F., et al.: J.A.M.A. **161**:46 (May 5) 1956. 2. Mitchell, E.H.: J.A.M.A. **161**:44 (May 5) 1956.

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SEPTEMBER, 1956

Merritt Becomes New President of ANA Succeeding Johannes M. Nielsen, H. Houston Merritt, professor of neurology at Columbia University and director of neurology at the New York Neurological Institute, became president of the American Neurological Association at the end of its 81st annual meeting, held at the Claridge Hotel, Atlantic City (June 18-20). Other officers elected were: Israel S. Wechsler, president-elect; Richard B. Richter, first vice-president; and Augustus S. Rose, second vice-president. Walter O. Klingman was elected member of the council for two years and Francis M. Forster was reelected as the association's representative to the American Board of Psychiatry and Neurology. Charles Rupp continues as secretary-treasurer and editor of the transactions, and William F. Caveness as assistant secretary.... Present at the meeting as distinguished guests were Professors Raymond Garcin of Paris and Mechislas A. Minkowski of Zurich, both of whom were elected to honorary membership. Also elected as honorary members were Detlev W. Bronk, Elizabeth C. Crosby, Herbert S. Gasser, and Ross G. Harrison. Ten new active members, four associate members, and one corresponding member (Shigeo Okinaka of Japan) were elected. ... The 1957 ANA meeting will be held at the Claridge Hotel, Atlantic City (June 16-18).

Magoun Receives Jacoby Award For his outstanding experimental work on the reticular formation, Horace W. Magoun received the third triennial Jacoby Award at the ANA meeting in Atlantic City. This award is made by the ANA to the member who, in the judgment of a committee appointed by the president, shall have achieved especially meritorious experimental work on any neurologic or psychiatric subject during the preceding three years. Previous recipients of the Jacoby Award were Percival Bailey and Wilder Penfield.... Provisions for this award were created by the will of the late Dr. George W. Jacoby, ANA vice-president (1905-06).

90 New Members Join Academy During June and July The campaign to add neurologists and neurologic scientists to the membership of the American Academy of Neurology added 46 new members in May (See Newsletter July 1956). During the months of June and July an additional 90 new members joined the Academy. These 90 new members (all cate-

gories) are: Harlow W. Ades, Matthew S. Atkinson, B. K. Bagchi, Berry Campbell, Norton Canfield, Leonard Carmichael, Max Chamlin, Irvin Chamovitz, David G. Cogan, Robert E. Cooke, Humberto M. Cravioto, Edward W. Dempsey, Derek Denny-Brown, John H. Dent, David D. Donaldson, Glenn A. Drager, Philip E. Duffy, Nicholson J. Eastman, William King Engel, Albert C. England, Jr., Irwin H. Feigin, Mary Jane Fina, L. W. Freeman, Alan J. Friedman, William C. Gibson, Wm. Henry Gordon, Pinckney J. Harman, Louis Hausman, Harold E. Himwich, David H. Hubel, W. R. Ingram, Robert B. Jackson, H. Worley Kendell, Alfred Kestenbaum, Gerald H. Klingon, Heinrich Kluver, Saul R. Korey, Wendell J. S. Krieg, E. Charles Kunkle, Alexander B. Leeds, Choh-luh Li, John C. Lilly, Donald B. Lindsley, Sarah A. Luse, Donald J. Lyle, Hugh N. A. MacDonald, Donald Macrea, Nathan Malamud, Wade H. Marshall, Elizabeth Mayrand, Fletcher McDowell, John T. McGrath, Francis L. McNaughton, Sedgwick Mead, Fred A. Mettler, David Nachmansohn, J. Olszewski, Leonard D. Osler, Richmond S. Paine, Benjamin Pasamanick, Frank Payne, Alfred Pope, Huntington Porter, Ruth Rhines, Flaviu S. A. Romanul, T. C. Ruch, Jonas E. Salk, George H. Schade, Arnold B. and Madge E. Scheibel, David W. Sinton, John deR. Slade, J. M. Sprague, Joseph B. Stevens, Ichiji Tasaki, Newman V. Treger, Robert D. Tschirgi, Betty Geren Uzman, Derrick Vail, John M. Van Buren, D. J. Vincent, Richard C. Wadsworth, Arthur A. Ward, James W. Ward, Robert Warner, Arthur L. Watkins, John R. Whittier, Harry H. Wilcox, Ernest H. Wood, Irving S. Wright.... Fellowship and active membership in the Academy are open to diplomates in neurology of the American Board of Psychiatry and Neurology, or to those certified in neurology by the Royal College of Physicians and Surgeons of Canada, who have been sponsored by two fellows or active members of the AAN. Junior membership is open to graduates of class A medical schools who are in residency training in neurology. Eligible for associate membership are those in advanced training in clinical neurology and physicians in other clinical fields or neurologic scientists who have made a contribution to the advancement of our knowledge of the nervous system.... Candidates for active or junior membership, with the proper sponsorship, should apply to Mrs. J. C. McKinley, AAN Executive Secretary, 3501 East 54th Street, Minneapolis 17, Minn. Candidates for fellowship or associate membership should apply to Dr. Pearce Bailey, Chairman, AAN Membership Committee, National Institute of Neurological Diseases and Blindness, Bethesda 14, Md.

Neuropathologists Elect New Officers At their annual meeting on June 17, which preceded the ANA meeting at the Claridge Hotel, Atlantic City, the American Association of Neuropathologists elected Ben Lichtenstein as president and K. Scharenberg, vice-president. Leon Roizin continues as secretary-treasurer, with offices at 722 West 168th Street, New York 32, N. Y.

EEG Colloquium To Be Held at Marseille

Under the direction of Professors G. Morin, W. Grey Walter, and Henri Gastaut, the European Reunion for Electroencephalographic Information will hold its seventh annual colloquium in Marseille, (Oct. 15-20). The principal subject to be discussed concerns the semiology and electroencephalographic manifestations of episodic psychic disturbances among epileptics which occur during seizure-free intervals. Under the presidency of Prof. Th. Alajouanine of Paris, about 25 specialists from this country and Europe will convene in Marseille for this meeting. Expected to attend from the United States are W. G. Lennox, W. T. Liberson, F. Ervin, A. W. Epstein, and Paul O. Maclean. Thursday morning, Oct. 18, has been set aside for a visit to the places frequented by Vincent Van Gogh, celebrated Dutch painter (1853-1890) who spent much of his life in the region Arles and Saint-Remy. After lunch on the same day, there will be an open discussion on the nature of Van Gogh's episodic psychic reactions, a subject of considerable neurologic controversy. On Saturday, Oct. 20, the colloquium will terminate with a presentation by Dr. Ludo van Bogaert, secretary-general of the First International Congress of Neurological Sciences, who will speak on anatomic, electroencephalographic, and clinical correlations in the necrotizing encephalitides and encephalitis associated with trypanosomiasis.... For further information on the colloquium, communications should be directed to Dr. R. Naquet, Laboratoire d'EEG, Hopital de la Timone, Marseille, France.

German Societies of Neurology Meet in Berlin

The German Society for Neurology, the German Society for Neurosurgery, and the German Electroencephalography Society will hold a combined meeting in Berlin (Sept. 19-22). Professor Olivecrona from Stockholm is the principal speaker, and has selected as his subject the Medical and Surgical Treatment of Epilepsy.... Inquiries about the meeting should be forwarded to Dr. Penzholz, Berlin-Charlottenburg. Spandauer Damm 130, Krankenhaus Westend.

Scandinavian Neurosurgical Society to Meet in Arhus

Dr. Bendt Broager, secretary of the Nordisk Neurokirurgisk Forening, announces that the twelfth annual meeting of the Scandinavian Neurosurgical Society will be held in Arhus, Denmark (Aug. 31-Sept. 1). In charge of the program is Prof. R. Malmros, Arhus kommunehospital, Denmark.

Multiple Sclerosis Society to Support Abstracting Service

The National Multiple Sclerosis Society has made an initial grant of $15,000 to the Excerpta Medica Foundation, Amsterdam, Holland. The foundation will excerpt from all current scientific and medical journals, foreign as well as American, material on demyelinating and related disorders. The results will be published in the monthly journal containing 100

to 150 abstracts and distributed among scientists, physicians, universities and libraries throughout the world. A ten-man editorial board of prominent scientists has been appointed to oversee the work. According to Dr. Frederick L. Stone, former medical and scientific director of the National Multiple Sclerosis Society, "It is all very well to have journals in German, Italian, or the Scandanavian languages in our libraries. All too often, however, our researchers are not familiar with the language or do not have the time to track down articles of importance. This abstracting service will, I believe, open up the world's literature on the demyelinating diseases to all who may be interested."... The $15,000 grant was accepted for the Excerpta Medica Foundation by its director, Peter A. Warren. Mr. Warren said that Dr. M. W. Woerderman will supervise the project, while Dr. G. W. F. Edgar will direct the actual abstracting and the staff in Amsterdam.

Act for the Construction of Research Facilities Signed by the President On July 30 President Eisenhower signed the Health Research Facilities Act of 1956, which authorizes the appropriation of funds, not to exceed 30 million dollars for each of three years, to assist in the financing of the construction of research facilities in "the sciences related to health," including medicine, public health, and their related basic sciences. The assistance consists of grants-in-aid to public and nonprofit institutions, on the basis of not more than 50 per cent for the Federal share. The funds are to be used to provide additional research facilities through the construction and/or equipping of new buildings or the expansion, remodeling, alteration, and/or equipping of existing buildings.... The Congress has now appropriated 30 million dollars to the Public Health Service for this program. The new law calls for the appointment of a National Advisory Council on Health Research Facilities which will meet in the near future to establish policy and the administration of the program.... Application forms and other information will be supplied promptly on request from the Division of Research Grants, National Institutes of Health, Public Health Service, Bethesda 14, Md.

Rose T Bailey

Products and Services

The information below was supplied by the manufacturers

ELIXIR BUTISERPINE

A new liquid dosage form of the antihypertensive and sedative, Butiserpine, has been introduced by McNeil Laboratories, Inc., Philadelphia. It is a highly palatable, yellow-colored preparation which can be readily adapted to a wide variety of prescription uses.

The elixir combines the intermediate sedative Butisol sodium, with the tranquilizer reserpine to augment the clinically established benefits produced by Butisol sodium alone. It is indicated in the treatment of mild to moderate essential hypertension, and for a mild sedative and tranquilizing effect in such conditions as coronary occlusion, angina pectoris, congestive heart failure, the anxiety neuroses, and insomnia.

Clinical use has demonstrated that Butiserpine can be administered over a long period of time without the hazard of accumulation associated with other barbiturates such as phenobarbital. Moreover, it provides safe and adequate control for the majority of patients with mild to moderate essential hypertension without the side effects produced by the more potent and antihypertensive drugs.

LORFAN—NARCOTIC ANTAGONIST

Hoffmann-La Roche Inc., Nutley, New Jersey, has just introduced Lorfan "Roche," a new narcotic antagonist for combating narcotic-induced respiratory depression. To date, Lorfan has had successful clinical trials in over 10,000 patients pre- and postoperatively, during surgery, during labor, in the newborn, and in the nonsurgical patient with severe pain.

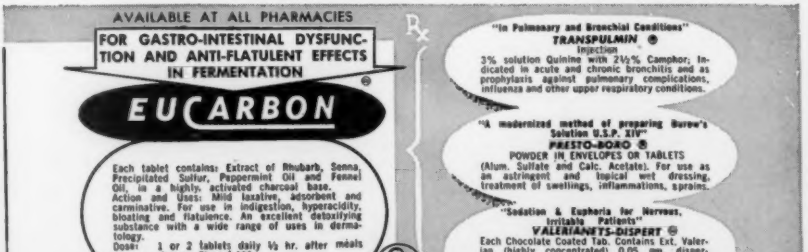
In appropriate dosage, Lorfan relieves respiratory depression without affecting analgesia, usually within one minute, the effect lasting two to five hours. However, Lorfan relieves respiratory depression only when it is due to narcotics; it does not affect other types of respiratory depression.

Lorfan tartrate (Roche brand of levallorphan tartrate) is available in a parenteral solution containing 1 mg. per cc. of l-3-hydroxy-N-allylmorphinan tartrate. It is packaged in 10 cc. multiple-dose vials. No narcotic blank is needed, since Lorfan is not a narcotic.

RESERPINE WITH MEBARAL

Reserpine with Mebaral, made by Winthrop Laboratories, New York, produces immediate and sustained tranquillity through two sites of central nervous system action—cortical and hypothalamic—permitting more effective management of anxiety and tension states. It does not impair mental efficiency. Neuromuscular tension is alleviated so that patients frequently sleep better without recourse to potent hypnotic agents. Psychotherapeutic approach to basic emotional difficulties is facilitated. In benign essential hypertension, control of emotional lability as well as gentle sustained antipressor action is obtained quickly. Blood pressure alterations in persons with normal pressure are rarely significant.

This preparation is useful for the management of anxiety and tension states, premenstrual tension, menopausal syndrome, as well as for essential hypertension, angina pectoris, and other disorders where an immediate and sustained tranquilizing effect is desirable.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When Wallace Laboratories, New Brunswick, New Jersey, brought out Miltown, one of the first of the tranquilizing drugs, little was said about the collateral benefits of its employment. Gradually these plus values are being disclosed by physicians who are studying its every effect. It is said to be "of considerable value" in alcoholism, by helping the patient avoid the serious symptoms that occur when alcohol is denied and also by helping him abstain following alcohol withdrawal. Miltown likewise appears to have some value in neurogenic conditions of the skin and in abdominal discomfort. Its greatest secondary virtue in the eyes of the neurologist is its value as an adjunct to psychotherapy by making patients more responsive to measures taken in their behalf. Several patients who have had emotional blocking in earlier psychotherapy sessions respond adequately after taking the tranquilizer, the feeling of ease and relaxation which Miltown brings about very definitely increasing the patient's confidence in the physician and breaking down his emotional defense. The drug seems least helpful in the treatment of severe depressive states, although more than half the patients of one group experiencing depression as part of other neurotic conditions were aided by Miltown.

In a study made more than a year ago all patients diagnosed as suffering primarily from a physical ailment or from neurological disorders were excluded. Patients who were overly psychotic were treated in the hospital, although some patients included in the study were felt to be on the border-line between an anxiety neurosis and a psychosis. The standard dose of Miltown was one 400 mg. tablet after each meal and at bedtime. In a few cases other drugs were given with Miltown. Duration of treatment with Miltown ranged from less than one month to more than eight months. It was reported that the new tranquilizer "was not found habit forming in the pharmacological sense and tolerance did not develop," making it useful for prolonged therapy.

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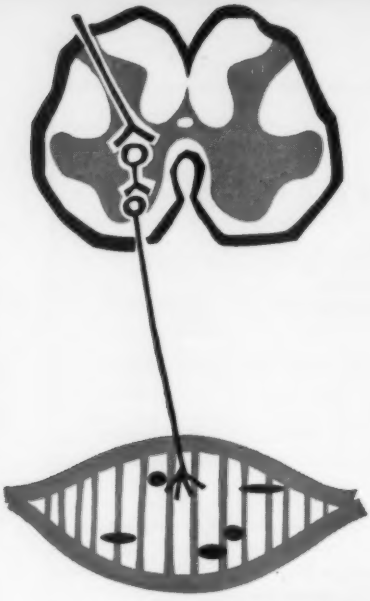

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Seven of 10 patients "...showed marked improvement in two to four weeks after initiation of therapy with the drug [FLEXIN]. In all of these, the improvement was objective."[2]

1. Abrahamsen, E. H., and Baird, H. W., III: J.A.M.A. *160*:749 (Mar. 3) 1956.
2. Rodriguez-Gomez, M.; Valdes-Rodriguez, A., and Drew, A. L.: J.A.M.A. *160*:752 (Mar. 3) 1956.

†U.S. Patent Pending

*T.M.

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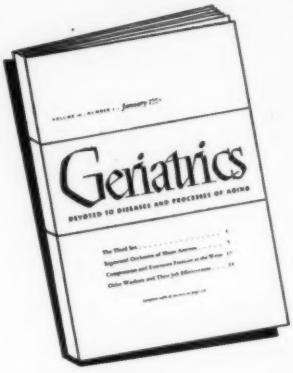

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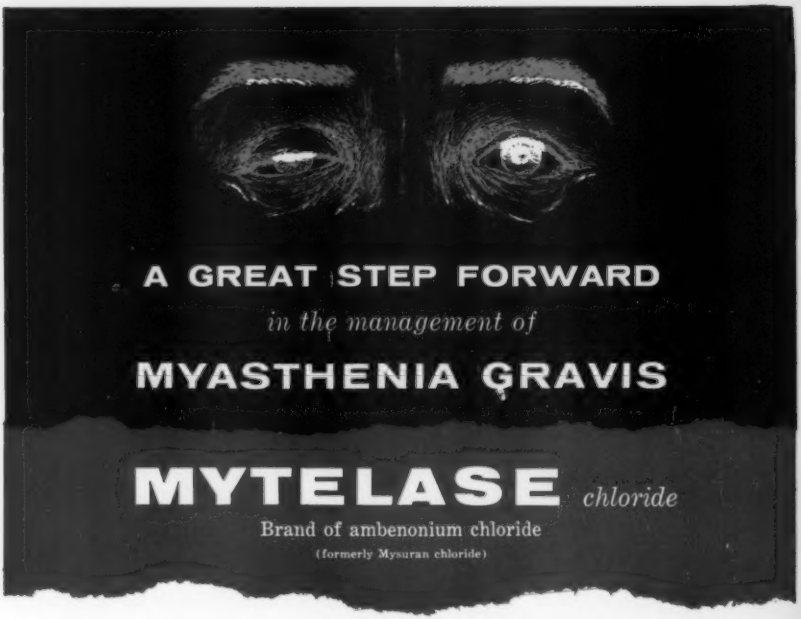

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1. Westerberg, Martha R.; and Magee, K.R.: Myasthenia Gravis. *Neurology*, 5:728, Oct., 1955. 2. Schwab, R.S.; Marshall, Clare K.; and Timberlake, William: Win 8077 in Treatment of Myasthenia Gravis. *J.A.M.A.*, 158:625, June 25, 1955. 3. Schwab, R.S.: Win 8077 in the Treatment of 60 Myasthenia Gravis Patients. *Am. Jour. Med.*, 19:734, Nov., 1955. 4. Schwab, R.S.: What Is New in Myasthenia Gravis. *Current Med. Digest*, 22:35, July, 1955.

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